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L18: Entry 12 of 34 File: PGPB Aug 8, 2002

PGPUB-DOCUMENT-NUMBER: 20020107502
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020107502 A1

TITLE: Apparatus, methods and kits for simultaneous delivery of a substance to multiple breast milk ducts

PUBLICATION-DATE: August 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	
He, Xuanmin	Palo Alto	CA	US	

US-CL-CURRENT: 604/506; 600/573, 604/74

CLAIMS:

What is claimed is:

1. A method for delivering a substance to two or more ductal networks in a breast, said method comprising: establishing access to two or more ductal network in the breast through a ductal orifice of each of said ductal network; and delivering a substance to and/or collecting a fluid simultaneously from two or more of the ductal networks.

2. A method as in claim 1, wherein establishing access comprises inserting an access probe in each ductal orifice to be accessed.

3. A method as in claim 2, wherein at least some of the access probes are fluidly connected by a manifold so that substance may be delivered simultaneously to the connected probes through the manifold.

4. A method as in claim 3, wherein all of the access probes are fluidly connected to the manifold so that fluid may be delivered simultaneously to all probes.

5. A method as in claim 1, wherein the substance is delivered simultaneously to all of the accessed ductal networks.

6. A method as in claim 1, wherein fluid is collected in separate receptacles for each ductal network.

7. A method as in claim 1, wherein access is established to all of the ductal networks in a breast.

8. A method for delivering a fluid to two or more ductal networks in a breast, said method comprising: locating two or more ductal networks in a nipple of the breast; inserting an access probe through an orifice of each of the located ductal networks; and infusing the fluid through a manifold to each of the probes.

9. A method as in claim 8, further comprising connecting individual probes to the manifold so that the number of probes connected to the manifold is the same as the number of probes inserted into ductal orifices.

10. A method as in claim 8, farther comprising providing an assembly comprising a number of access probes greater than the number of ductal orifices, wherein said access probes are pre-loaded on the manifold, and selectively blocking those access probes connected to the manifold which are not inserted to a ductal network.

11. A method as in claim 8, further comprising collecting fluid from each accessed ductal network, wherein the fluid is collected separately so that no one fluid from a ductal network is mixed with fluid from another ductal network.

12. A kit for delivering a substance to two or more ductal networks in a breast, said kit comprising: a two or more of probes each having a lumen and being configured for introduction into a ductal network of the breast, and instructions for use setting forth a method according to any of claims 1-11.

13. A method for delivering a fluid to two or more ductal networks in a breast, said method comprising the steps of: locating at least two ductal networks in a nipple of the breast; providing an apparatus having a plurality of ductal network access probes; inserting one of the access probes through an orifice of each of the located ductal networks; closing any of the access probes that do not access one of the ductal networks; and infusing the fluid through a manifold of said apparatus to each of the probes that accesses one of the ductal networks.

14. A method as in claim 13, further comprising the step of controlling a fluid flow through collection lumens, each said collection lumen being connected at a distal end to one of the probes that accesses one of the ductal networks and at a proximal end to a separate collection receptacle.

15. A method as in claim 14, further comprising the step of collecting fluid in a respective one of the separate collection receptacles for each accessed duct.

16. A method as in claim 14, wherein the step of controlling a fluid flow through collection lumens comprises: closing fluid flow valves in the collection lumens corresponding to the access probes inserted in the ductal networks while fluid is infused into the accessed ductal networks; closing back flow valves in the access probes corresponding to the collection lumens; and opening the fluid flow valves for the collection lumens corresponding to the access probes inserted in the ductal networks to permit fluid from the ductal networks to flow through the collection lumens and into the collection receptacles.

17. A method as in claim 16, further comprising massaging the breast just before and/or after the step of opening the fluid flow valves in the collection lumens.

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L18: Entry 9 of 34 File: PGPB Oct 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020142941
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020142941 A1

TITLE: Intraductal treatment targeting methylated promoters in breast cancer

PUBLICATION-DATE: October 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	

US-CL-CURRENT: 514/1

CLAIMS:

What is claimed is:

1. A composition for administration into a breast duct of a patient having abnormal breast ductal epithelial cells including atypical or malignant cells in said breast duct; said composition comprising: a methylation modulating agent; and a biocompatible solution suitable as a vehicle for delivering the methylation modulating agent into the breast duct of the patient, wherein the composition is delivered into the breast duct of the patient and contacts breast duct epithelial cells therein.

2. The composition of claim 1 wherein the methylation modulating agent is selected from the group consisting of an inhibitor of DNA methylation, a demethylating agent, and an antagonist of DNA methyl transferase activity.

3. The composition of claim 1 wherein the methylation modulating agent modulates methylation or demethylation at CpG sites on promoters for breast cancer-related genes.

4. The composition of claim 3 wherein the breast cancer-related genes are selected from the group consisting of cyclin D2, RARbeta2, twist, BRCA1, maspin, estrogen receptor, progesterone receptor, e-cadherin, p16 (INK4a), P15 (INK4b), P14 (ARF), death associated protein (DAP), retinoblastoma Rb, and vonHippel-Lindaur (VHL) gene.

5. The composition of claim 1 wherein the methylation modulating agent is a demethylating agent.

6. The composition of claim 1 wherein the methylation modulating agent is a DNA methylation inhibitor.

7. The composition of claim 6 wherein the DNA methylation inhibitor competitively binds methyl groups and prevents methylation at cytosines.

8. The composition of claim 6 wherein the DNA methylation inhibitor is an oligonucleotide directed against a CpG island region of a promoter of a breast cancer related gene.

9. The composition of claim 1 wherein the methylation modulating agent is a DNA methyl transferase antagonist.

10. The composition of claim 9 wherein the DNA methyl transferase antagonist catalyzes the methylation reaction at cytosine residues of 5-aza-2-deoxycytidine (5-aza-CdR).

11. The composition of claim 1 wherein the biocompatible solution is selected from the group consisting of saline, viscous material, and gel material.

12. A method for treating a patient having premalignant or malignant breast duct epithelial cells in a breast duct, the method comprising: delivering a composition into the breast duct of the patient, said composition comprising a methylation modulating agent and a biocompatible solution suitable as a vehicle for delivering the methylation modulating agent into the breast duct of the patient; modulating DNA methylation of breast cancer-related genes within said premalignant or malignant breast duct epithelial cells.

13. The method of claim 12 wherein the methylation modulating agent is selected from the group consisting of an inhibitor of DNA methylation, a demethylating agent, and an antagonist of DNA methyl transferase activity.

14. The method of claim 12 wherein the breast cancer-related genes are selected from the group consisting of cyclin D2, RARbeta2, twist, BRCA1, maspin, estrogen receptor, progesterone receptor, e-cadherin, p16 (INK4a), P15 (INK4b), P14 (ARF), death associated protein (DAP), retinoblastoma Rb, and vonHippel-Lindaur (VHL) gene.

15. The method of claim 12 wherein the methylation modulating agent is a demethylating agent.

16. The method of claim 12 wherein the methylation modulating agent is a DNA methylation inhibitor.

17. The method of claim 16 wherein the DNA methylation inhibitor competitively binds methyl groups and prevents methylation at cytosines.

18. The method of claim 16 wherein the DNA methylation inhibitor is an oligonucleotide directed against a CpG island region of a promoter of a breast cancer related gene.

19. The method of claim 12 wherein the methylation modulating agent is a DNA methyl transferase antagonist.

20. The method of claim 19 wherein the DNA methyl transferase antagonist catalyzes the methylation reaction at cytosine residues of 5-aza-2-deoxycytidine (5-aza-CdR).

21. The method of claim 12 wherein the biocompatible solution is selected from the group consisting of saline, viscous material, and gel material.

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L18: Entry 3 of 34 File: PGPB Feb 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030039959
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030039959 A1

TITLE: METHODS FOR IDENTIFICATION, DIAGNOSIS, AND TREATMENT OF BREAST CANCER

PUBLICATION-DATE: February 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
LOVE, SUSAN	PACIFIC PALISADES	CA	US	
NIKOLCHEV, JULIAN	PORTOLA VALLEY	CA	US	
HUNG, DAVID	BELMONT	CA	US	

US-CL-CURRENT: 435/6; 435/7.23

CLAIMS:

What is claimed is:

1. A method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, said method comprising: providing a targeting molecule coupled to an identifying agent; and delivering the coupled compound through a preselected individual breast duct in an amount sufficient to identify premalignant or malignant cancerous cells.

2. A method as in claim 1, wherein delivering comprises cannulation or catheterization of the breast duct.

3. A method as in claim 1, wherein the coupled compound is delivered to more than one duct on a breast.

4. A method as in claim 1, wherein the cells are identified for the purpose of excising tissue surrounding and including the cells.

5. A method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, said method comprising: providing a identifying agent; and delivering the identifying agent through a preselected individual breast duct in an amount sufficient to identify premalignant or malignant cancerous cells.

6. A method as in claim 5, wherein delivering comprises cannulation or catheterization of the breast duct.

7. A method as in claim 5, wherein the identifying agent is delivered to more than one duct on a breast.

8. A method as in claim 5, wherein the cells are identified for the purpose of excising tissue surrounding and including the cells.

9. A method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising: providing an identifying agent coupled to a targeting agent; and delivering the coupled

compound through a preselected individual breast duct in an amount sufficient to detect lymph node involvement.

10. A method as in claim 9, wherein detecting lymph node involvement comprises detecting the identifying agent coupled to a targeting agent in a sentinel lymph node.

11. A method as in claim 9, wherein delivering comprises cannulation or catheterization of the breast duct.

12. A method as in claim 9, wherein the identifying agent coupled to a targeting agent is delivered to more than one duct on a breast.

13. A method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising: providing a identifying agent; and delivering the identifying agent through a preselected individual breast duct in an amount sufficient to detect lymph node involvement.

14. A method as in claim 13, wherein detecting lymph node involvement comprises detecting the identifying agent in a sentinel lymph node.

15. A method as in claim 13, wherein delivering comprises cannulation or catheterization of the breast duct.

16. A method as in claim 13, wherein the identifying agent is delivered to more than one duct on a breast.

17. A method of treating premalignant or malignant breast cancer, said method comprising: providing a targeting molecule coupled to a therapeutic agent; and delivering the coupled compound through a preselected individual breast duct in an amount sufficient to inhibit proliferation of the cancerous cells.

18. A method as in claim 17, wherein delivering comprises cannulation or catheterization of the breast duct.

19. A method as in claim 17, wherein the coupled compound is delivered to more than one duct on a breast.

20. A method as in claim 17, wherein the targeting agent comprises an agent selected from the group consisting of a protein, a polypeptide, a peptide, an antibody, an antibody fragment, a ligand, a receptor, a drug, a chemical, a lipid, a liposome, a small molecule, and a nucleic acid.

21. A method as in claim 17, wherein the therapeutic agent is selected from the group consisting of a cytotoxic agent, a cytolytic agent, a growth inhibiting agent, an antagonist, an agonist, and a drug or agent containing liposome.

22. A method as in claim 17, wherein the therapeutic agent comprises an agent with therapeutic activity against cancerous or precancerous cells that can be coupled to a targeting agent.

23. A method of treating a premalignant or malignant breast cancer, said method comprising: providing a targeting molecule itself having therapeutic activity; and delivering the targeting molecule through a preselected individual breast duct in an amount sufficient to inhibit proliferation of the cancerous cells.

24. A method as in claim 23, wherein delivering comprises cannulation or catheterization of the breast duct.

25. A method as in claim 23, wherein the targeting molecule is delivered to more than one duct on a breast.

26. A method as in claim 23, wherein the targeting molecule comprises an agent selected from the group consisting of a protein, a polypeptide, a peptide, an antibody, an antibody fragment, a ligand, a receptor, a drug, a chemical, a lipid, a

liposome, a small molecule, and a nucleic acid.

27. A method as in claim 23, wherein the therapeutic activity is selected from the group consisting of a cytotoxicity, a cytolytic activity, growth inhibition, antagonism, an agonism, and immunotoxicity.

28. A method as in claim 23, wherein the therapeutic activity is effective against cancerous or precancerous cells.

29. A method as in claim 17 or 23, wherein the premalignant or malignant breast cancer comprises cells having a stage selected from the group consisting of hyperplasia, atypical hyperplasia, low-grade ductal carcinoma in situ, high-grade ductal carcinoma in situ, and invasive carcinoma.

30. A kit for localizing or treating lesions in a breast duct, said kits comprising: at least one catheter configured to access a ductal network in a human breast; and instructions for use setting forth a method according to any of claims 1 to 28.

31. A kit as in claim 30, further comprising at least one container holding a reagent which is used in the method being performed with the kit.

32. A kit as in claim 30, further comprising a package holding the catheter and the instructions for use.

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L18: Entry 4 of 34 File: PGPB Jan 30, 2003

PGPUB-DOCUMENT-NUMBER: 20030022161
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030022161 A1

TITLE: Identifying, monitoring, and treating women for breast precancer or cancer

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Love, Susan	Pacific Palisades	CA	US	
Hung, David	Belmont	CA	US	
Cen, Hui	Oakland	CA	US	

US-CL-CURRENT: 435/6; 424/155.1, 435/7.23

CLAIMS:

What is claimed is:

1. A method of screening women for breast cancer or precancer said method comprising: providing a ductal fluid sample from at least one duct of a breast of the patient; and determining in the sample a level of a marker selected from the group consisting of aromatase enzyme, aromatase activity, a biproduct of estrogen synthesis and a protein effector acting upstream of estrogen synthesis; wherein a detectable level above a normal value indicates an increased risk for breast cancer or precancer.

2. A method as in claim 1, further comprising detecting one or more precancerous or cancerous ductal epithelial cells in the sample; wherein the presence of precancerous or cancerous cells indicates that the patient has an increased chance of benefiting from administration of an estrogen activity modulator.

3. A method as in claim 2, wherein detecting comprises detecting cells as a stage selected from the group consisting of ductal hyperplasia, atypical ductal hyperplasia, and low grade ductal carcinoma in situ (LG-DCIS).

4. A method as in claim 2, wherein detecting comprises detecting cells as a stage selected from the group consisting of high-grade ductal carcinoma in situ (HG-DCIS) and invasive carcinoma.

5. A method as in claim 1 or 2, further determining in the sample a level of estrogen or estrogen metabolite, wherein the level above normal indicates a risk for developing abnormal cells in the duct.

6. A method as in claim 2 or 5, further comprising examining any abnormal cells to detect the presence of an estrogen receptor on the surface, wherein the presence of the estrogen receptor indicates that the cell is hormone responsive.

7. A method as in claim 1, wherein the woman is postmenopausal and on hormone replacement therapy (HRT).

8. A method as in claim 7, further comprising detecting precancerous or cancerous

ductal epithelial cells in the sample; wherein the presence of precancerous or cancerous ductal epithelial cells indicates that the patient has an increased chance of benefiting from at least one administration of an estrogen activity modulator, stopping the HRT, reducing the dosage of hormone in the HRT, and/or switching to a different hormone or agent for treating menopausal symptoms or osteoporosis.

9. A method as in claim 8, further comprising determining in the sample a level of estrogen or estrogen metabolite, wherein a level above normal indicates an increase risk for developing cancer or precancer in the breast.

10. A method as in claim 8 further examining any abnormal cells to detect the presence of an estrogen receptor on the surface, wherein the presence of the estrogen receptor indicates that the cell is hormone responsive.

11. A method as in claim 8, wherein the action selected comprises administration of an estrogen activity modulator, and the estrogen activity modulator is administered intraductally to an affected duct or ducts.

12. A method as in claim 1, wherein providing the ductal fluid sample comprises obtaining the sample from the breast.

13. A method as in claim 1, wherein providing the ductal fluid comprises receiving a sample that has been previously obtained.

14. A method as in claim 1, wherein the fluid was obtained by nipple aspiration or by ductal lavage of at least one breast milk duct.

15. A method as in claim 2 or 8 wherein examining the ductal fluid sample comprises cytological examination of ductal epithelial cells.

16. A method of treating a woman who has been determined to have one or more precancerous or cancerous ductal epithelial cells in a breast duct and an elevated level of a marker selected from the group consisting of aromatase enzyme, aromatase activity, a biproduct of estrogen synthesis, and a protein acting upstream of estrogen synthesis in a ductal fluid sample said method comprising: administering at least one dose of an aromatase inhibitor to the woman.

17. A method as in claim 16, wherein the aromatase inhibitor comprises an agent selected from the group consisting of toremifene, anastrozole, letrozole, fadrozole, lentaron, formestane, and rivizor.

18. A method as in claim 16, wherein administrating comprises intraductal delivery of the aromatase inhibitor.

19. A method as in claim 18, wherein the intraductal delivery comprises accessing the breast duct with a ductal access device and delivering the aromatase inhibitor.

20. A method as in claim 18, wherein the aromatase inhibitor comprises a time release formulation.

21. A method of treating a woman who has been determined to have one or both of (a) precancerous or cancerous ductal epithelial cells in a breast duct, and (b) an increased level of estrogen or estrogen metabolite in a ductal fluid sample comprising: administering at least one dose of an estrogen activity modulator intraductally.

22. A method as in claim 21, wherein the estrogen activity modulator is selected from the group consisting of an estrogen antagonist, an aromatase inhibitor, a selective estrogen receptor modulator, a modulator of a protein effector acting upstream of estrogen synthesis, and a cocktail of estrogen activity modulators.

23. A method of screening patients for postmenopausal hormone replacement therapy (HRT), said method comprising: providing a ductal fluid sample from at least one duct of a breast of the patient, and examining the ductal fluid sample for the presence of a precancerous or cancerous ductal epithelial cell; wherein HRT is

contradicted in patients having precancerous or cancerous ductal epithelial cells in the ductal fluid sample.

24. A method as in claim 23, wherein the precancerous ductal epithelial cell comprises a cell at a stage selected from the group consisting of ductal hyperplasia, atypical ductal hyperplasia, and low grade ductal carcinoma in situ (LG-DCIS).

25. A method as in claim 23, wherein the cancerous ductal epithelial cell comprises a cell at a stage selected from the group consisting of high grade ductal carcinoma in situ (HG-DCIS) and invasive carcinoma.

26. A method as in claim 23, further comprising determining in the sample a level of a marker selected from the group consisting of aromatase enzyme, aromatase activity, estrogen, estrogen metabolite, a biproduct of estrogen synthesis, and a protein acting upstream of estrogen synthesis in a ductal fluid, wherein a level above normal indicates an increased risk for developing cancer or precancer in the breast.

27. A method as in claim 23 or 26, further comprising examining the cancerous or precancerous ductal epithelial cells to detect the presence of an estrogen receptor, wherein the presence of the estrogen receptor indicates that the cell is hormone responsive.

28. A method as in claim 23, wherein the patient is surgically postmenopausal.

29. A method as in claim 26 or 27, further comprising detecting precancerous or cancerous ductal epithelial cells in the sample, wherein the presence of precancerous or cancerous ductal epithelial cells indicates the patient has an increased chance of benefiting from at least one of administration of a lower dosage of hormone in the HRT, close monitoring of markers and ductal epithelial cell changes while the patient is on HRT, selecting an agent for HRT that provides a reduced breast cancer risk, not placing the patient on HRT, and administering an estrogen activity modulator to an affected duct or ducts intraductally.

30. A method as in claim 29, wherein when a marker is increased, and the ductal epithelial cells are normal, the patient is placed on HRT and monitored periodically for changes in marker levels and ductal epithelial cells.

31. A method as in claim 23, wherein providing the ductal fluid sample comprises obtaining the sample from the breast.

32. A method as in claim 23, wherein providing the ductal fluid sample comprises receiving a sample which has been previously obtained.

33. A method as in claim 23, wherein the fluid was obtained by nipple aspiration or by ductal lavage of at least one milk duct.

34. A method as in claim 23, wherein the fluid is collected from a single duct.

35. A method as in claim 23, wherein examining the ductal fluid comprises cytological examination of ductal epithelial cells in the sample to determine whether they are precancerous or cancerous.

36. A method of monitoring a menopausal or postmenopausal woman on hormone replacement therapy (HRT) comprising: providing a ductal fluid sample from one or more ducts of a breast of a patient, and examining the ductal fluid sample for a precancerous or cancerous ductal epithelial cell, wherein indicated therapies for patients found to have one or more precancerous or cancerous epithelial cells include stopping HRT, reducing a dosage of hormone in the HRT, taking an estrogen activity modulator systemically, taking an estrogen activity modulator intraductally, switching to a different drug to reduce menopausal symptoms, and switching to a different drug to reduce bone loss.

37. A method as in claim 36, wherein the precancerous ductal epithelial cell comprises a cell at a stage selected from the group consisting of ductal

hyperplasia, atypical ductal hyperplasia, and low grade ductal carcinoma in situ (LG-DCIS).

38. A method as in claim 36, wherein the cancerous ductal epithelial cell comprises a cell at a stage selected from the group consisting of high grade ductal carcinoma in situ (HG-DCIS) and invasive carcinoma.

39. A method as in claim 36, further comprising examining the precancerous or cancerous ductal epithelial cells to detect the presence of an estrogen receptor, wherein the presence of an estrogen receptor indicates that the cell is hormone responsive.

40. A method as in claim 36, wherein the action selected comprises taking an estrogen activity modulator, and the estrogen activity modulator is administered intraductally.

41. A method as in claim 40, wherein the estrogen activity modulator comprises an aromatase inhibitor.

42. A method as in claim 36 or 39, further comprising assaying the ductal fluid for an elevated level of a marker selected from the group consisting of estrogen, an estrogen metabolite, aromatase enzyme, evidence of aromatase activity, biproducts of estrogen synthesis, and a protein effector acting upstream of estrogen synthesis; wherein indicated therapies for patients having an elevated level of one or more markers above normal include administration of a lower dosage of hormone in the HRT, close monitoring of markers while the patient is on HRT, close monitoring of ductal epithelial cell changes while the patient is on HRT, selecting an agent for HRT that provides a reduced cancer risk, stopping the HRT, and intraductal administration of an estrogen activity modulator to an affected duct or ducts.

43. A method as in claim 42, wherein when a marker is elevated above normal, and the ductal epithelial cells are normal, the patient is directed to remain on HRT and be monitored periodically for changes in marker levels and ductal epithelial cell character.

44. A method as in claim 36, wherein providing the ductal fluid sample comprises obtaining the sample from the breast.

45. A method as in claim 36, wherein providing the ductal fluid sample comprises receiving a sample which has been previously obtained.

46. A method as in claim 36, wherein the fluid was obtained by nipple aspiration or by ductal lavage of at least one milk duct.

47. A method as in claim 36, wherein the fluid is collected from a single duct.

48. A method as in claim 36, wherein examining the ductal fluid comprises cytological examination of ductal epithelial cells in the sample to determine whether they are precancerous or cancerous.

49. A method of treating a peri-, menopausal, or postmenopausal woman for both cancer risk and reduction of menopausal symptoms, osteoporosis, or cardiovascular risk wherein the peri-, menopausal, or postmenopausal woman has been found to have an elevated level of a marker selected from the group consisting of estrogen, an estrogen metabolite, aromatase enzyme, aromatase activity, a biproduct of estrogen synthesis, and a protein acting upstream of estrogen synthesis in a ductal fluid, said method comprising: systemically administering estrogen hormone, and locally administering an estrogen activity modulator to breast milk ducts that display an elevated level of one or more markers.

50. A method as in claim 49, wherein locally administering an estrogen activity modulator comprises intraductal administration.

51. A method as in claim 49, wherein the estrogen activity modulator comprises an estrogen antagonist, an aromatase inhibitor, or a cocktail of estrogen activity

modulators.

52. A method as in claim 51, wherein the estrogen activity modulator is an aromatase inhibitor selected from the group consisting of toremifene, anastrozole, letrozole, fadrozole, lentaron, formestane and rivizor.

53. A method as in claim 49, further comprising monitoring one or more breast ducts of the patient for precancerous or cancerous ductal epithelial cells at time points selected from the group consisting of before, during, and after the systemic estrogen administration.

54. A kit comprising a device for retrieving a ductal fluid sample from a breast duct and instructions for use setting forth a method according to any of claims?

55. A kit as in claim 54, further comprising a therapeutic agent for intraductal delivery to a patient, wherein the therapeutic agent comprises an estrogen activity modulator.

56. A kit as in claim 55, wherein the estrogen activity modulator comprises an aromatase inhibitor.

57. A kit as in claim 54, further comprising a therapeutic agent for intraductal delivery to a patient, wherein the therapeutic agent comprises an estrogen activity modulator.

58. A kit as in claim 57, wherein the estrogen activity modulator comprises an aromatase inhibitor.

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L2: Entry 4 of 12 File: PGPB Dec 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020193339
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020193339 A1

TITLE: Antiviral agent for use in treatment of cancer

PUBLICATION-DATE: December 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bourhis, Jean	Sceaux		FR	
Abdulkarim, Bassam	Vanves		FR	
Deutsch, Eric	Paris		FR	

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	COUNTRY	TYPE CODE
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APPL-NO: 10/ 138999 [PALM]
DATE FILED: May 2, 2002

RELATED-US-APPL-DATA:
Application 10/138999 is a continuation-of US application PC/T/EP00/11246, filed November 3, 2000, UNKNOWN

FOREIGN-APPL-PRIORITY-DATA:

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INT-CL: [07] A61 K 31/7076, A61 K 31/7072
US-CL-PUBLISHED: 514/46; 514/51
US-CL-CURRENT: 514/46; 514/51

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

The invention relates to an antiviral agent for use in combination with an anticancer agent, for the treatment of cancer. Especially, the invention provides means for the treatment of non-virus-associated cancer.

[0001] The present invention relates to the field of the treatment of cancer and especially involves the use of antiviral agents for the treatment of cancer. The invention relates to the treatment of virus-associated cancer, or non-virus-associated cancer.

[0002] In studying various human tumor cell lines derived from virus-associated cancers, the inventors have shown that antiviral agents used in combination with other therapeutic agents, may provide a new way for the treatment of cancer, with improved sucess in controlling the development of the tumor. The inventors have also

shown that said combination of an antiviral agent with another therapeutic agent may also be used advantageously in the treatment of non virus-associated cancers.

[0003] Although there has been no direct relationship established between a detected viral infection and the occurrence of cancer in human, studies have shown in the past that virus infection can be a co-factor frequently associated with carcigonenesis in infected cells and as a consequence can be linked to the development of malignant lesion and in general related with the development of cancer.

[0004] In these situations where an infection by a virus can be correlated with the development of malignancy especially in the human body, it is believed that other contributing factors may also be involved.

[0005] To date, it appears that human cancers, associated with virus infection are mainly represented by lymphomas and carcinomas. For example, infection by the Epstein-Barr virus (EBV) has been detected in nasopharyngeal carcinomas, Burkitt and other lymphomas, papillomavirus infection (HPV) has been shown to be involved in some head and neck carcinomas, and uterine cervix carcinomas, infections by Hepatitis B or C viruses have been associated with the occurrence of hepatocarcinomas.

[0006] These virus-associated cancers, where viral infection is a co-factor involved in the carcinogenesis of human cancer represent 15 to 20% of the whole number of cancers in the world (26,27).

[0007] From a general point of view, cancers, including virus-associated cancers, are treated through different ways. It is especially well-known that cancer treatment comprises surgery, radiation and chemotherapy. More recently immunotherapy has been introduced as a further available treatment regimen. It is also noted that cancers may be treated, if appropriate, with a combination of several of these available treatments. Therefore, the above-cited treatment regimens can be viewed as constituting a primary therapy or depending upon the specific cases, as an adjudant therapy.

[0008] As far as virus-associated cancers are concerned, it is noted that conventional treatments of the type of the above-cited treatment, have shown a relatively high level of failure to cure or improve the situation of the patients, especially in locally advanced disease (40-60% failure in stage III-IV nasopharyngeal carcinoma and in stage III carcinoma of the uterine cervix (27)).

[0009] Therefore, new approaches for therapeutic treatment of cancers are desirable. Such an alternative or complementary possibility of treatment of cancers is provided by the inventors through the definition of means involving the use of antiviral agents.

[0010] Interestingly, the efficiency which has been observed by the inventors on the control of tumors associated with viral infection, when using antiviral agents, has also been shown unexpectedly on non virus-associated cancers.

[0011] In a publication (1), Andrei G. et al (<<Inhibiting Effect of Cydofovir (HPMPC) on the Growth of the Human Cervical Carcinoma (SiHa) Xenografts in Athymic Nude Mice>>), have disclosed that in view of a strong association noticed between infection with specific genital viruses (HPV viruses) and the development of cervical cancer, an assay was made, to treat cell lines derived from human cervical carcinoma with HPMPC ([(S)-1-[3-hydroxy-2-(phosphonomatoxy)propyl]cytosine, Cidofovir) which is known to be an antiviral agent.

[0012] As a result of this experimental work, Andrei et al (1) have shown that cell proliferation of these cell lines was inhibited in a concentration-dependent and in a time-dependent fashion. They further report that effects of HPMPC on the growth of cervical carcinoma xenografts in athymic nude mice has been observed, allowing to conclude that animals that were injected intratumorally with HPMPC at a certain dose, have shown statistically significant reduction in tumor size compared to a placebo group or to a group of animals treated with another specific antiviral

agent. They further state that, when HPMPC was administered topically or systemically, no reduction of tumor growth was observed when nontoxic concentrations of the compound were used.

[0013] Within the frame of the present invention, the inventors have observed that contrary to what has been concluded by Andrei et al in the above-cited publication, HPMPC, among other antiviral agents, can be used for the treatment of cancer and especially by using non toxic systemic concentrations. Both virus-associated cancers and non virus-associated cancers may be treated by the use of antiviral agent in appropriate conditions defined in the present invention.

[0014] The inventors provide means for the treatment of cancer, that comprise the use of antiviral agents in combination with known groups of anticancer agents, said combination enabling a synergic effect to occur between the antiviral agent and the anticancer agent. It is stated that anticancer agents implicated in the production of this synergic effect include conventional anticancer agents among those used for the anticancer conventional therapy cited hereabove.

[0015] The present invention therefore relates to a method of treatment of cancer, which comprises the steps of:

[0016] administering to a patent in need thereof an anticancer agent and

[0017] administering to said patient an antiviral agent.

[0018] Each of the features described hereafter for the definition of the type of cancer to be treated or in relation to the nature or use of the anticancer agent or of the antiviral agent is applicable for the implementation of said method of treatment.

[0019] The sequences of administration of said anticancer and said antiviral agents are defined by the skilled person.

[0020] According to the invention, the expression <<synergic effect>> signifies that the effect obtained with the combination of several agents within the scope of the invention is higher than the effect which is obtained with only one of these agents or, advantageously the effect which is obtained with the combination of the above said agents is higher than the addition of the effects obtained with each of these agents used separately.

[0021] Accordingly, the inventors have shown that antiviral agents can be used in combination with other groups of molecules, compositions, or irradiation treatments used as anti-cancer agents for the treatment of cancer, and especially for the treatment of virus-associated cancers, thereby producing an improved effect on the tumor development.

[0022] In the present invention, the expression <<antiviral agents>> relates to agents having an interaction effect and for instance an inhibitory effect on the infection of cells by a virus. Within the possible effects of said antiviral agents, one may include the capacity of the antiviral agent to inhibit the infection of the host cells by the virus and/or to inhibit the replication of the virus or the proliferation of the virus in host cells. Additionally or alternatively, the antiviral agents of the invention are agents which can have a direct effect on the infected host cells including for instance against their transformation towards a malignant state.

[0023] For the purpose of the invention, an antiviral agent which appears to produce a result in the treatment of cancer, when combined with an anticancer agent as defined hereafter, is designated as an antiviral agent.

[0024] By the expression <<anticancer agent>> is meant according to the present invention, any known agent or agent to be developed which has, in proper conditions, an activity on the formation of a malignant lesion and/or on the growth or on the spreading of the formed malignant lesion towards the formation, growth and spreading of the tumor.

[0025] In other words, it is pointed out that, according to the invention, an anticancer agent can interfere with the process of malignant transformation of a normal cell and/or with the development or spreading of the tumor. In some cancers, anticancer agents can interfere with abnormal cell differenciation or metastases.

[0026] It is also emphasized that, the definition of the anticancer agent applies to agents having effects on the control of the biologic and/or biochemical basis for cancer disease, or on the control of the clinical progress of the disease or recurrence thereof. In a particular embodiment, the anticancer agent is able to cure the cancer disease.

[0027] The expression <<treatment of cancer>> according to the invention, can be construed as encompassing the effect that is normally sought with an anticancer agent, as defined above. Advantageously, it encompasses the effect which can be obtained on malignant cells or on developed tumors, following administration of the combination of the antiviral-agent and the anticancer agent. Especially it encompasses reduction in tumor size, which can be measured in accordance with the assays provided in the examples of this patent application.

[0028] The word <<combination>> which is used according to the invention, designates the use of the antiviral agent and of the anticancer agent in the treatment of a detected cancer either a virus-associated cancer or a non virus-associated cancer. In a particular embodiment of the invention, it encompasses the associated use of both agents if they can be used together, for instance in the same composition. Alternatively, it designates the separated administration of these agents. Said <<separated>> administration includes the simultaneous, concomitant or sequential administration in time, either as a consequence of the difference in physical or chemical nature of the agents or as a result of the regimen or schedule of treatment requiring that the agent be used separately in time, or be used through separated routes of administration.

[0029] Antiviral agents or anticancer agents are as a consequence proposed for use in treatment of cancer, when they are capable, in combination, to produce an interaction effect on the occurrence or on the development of a malignant lesion and/or on the occurrence or on the development of the resulting tumor.

[0030] According to a particular embodiment, the invention relates to the use of an antiviral agent replying to one or several of the various definitions provided in the present application, for the manufacture of a drug for the treatment of a cancer either of a virus-associated cancer or of a non-virus-associated cancer, wherein said drug is used in combination with an anti-cancer agent.

[0031] The invention also relates to the use of an antiviral agent for the manufacture of a drug suitable for the treatment by systemic route of a cancer, in accordance with the above-given definitions.

[0032] Accordingly, in a particular embodiment, the invention relates to a method for the treatment of cancer comprising the steps of

[0033] administering an antiviral agent through the systemic route, to a patient in need thereof,

[0034] administering to said patient, an anticancer agent.

[0035] Depending on its nature and properties, the anticancer agent can also be administered through the systemic route. Alternatively, it can be provided to the patient through another route, especially locally.

[0036] Among the antiviral agents which can be used according to the invention, antiviral agents which are non-specific for a particular virus or for a determined group of viruses, are of particular interest.

[0037] In a particular embodiment, the invention relates to an antiviral agent as defined according to the invention, for use in appropriate conditions, wherein this

agent is chosen among compounds or compositions having a broad spectrum antiviral activity.

[0038] Antiviral agents may be classified in several groups which may sometimes overlap, depending on the parameters which are used for the classification.

[0039] The specificity of the antiviral agent with respect to a particular type of virus, or to the contrary with regard to its activity against a broad spectrum of viruses, may be one of the possibilities of classification of these agents.

[0040] It is also noted in accordance with the invention, that the antiviral agents can be chosen with respect to their capacity to interact with the targeted virus or with the host cells, especially when the treated cancer is associated with viral infection.

[0041] In a particular embodiment, the invention relates to an antiviral agent replying to one or several aspects of the definitions given above, for use in the treatment of cancer, wherein this antiviral agent has a cytotoxic activity on the cells infected by the virus.

[0042] In addition or alternatively, the antiviral agent used in accordance with the present invention is an antiviral agent capable of inhibiting viral polymerases and/or cellular polymerases.

[0043] Advantageously, the invention proposes the use of antiviral agents for the treatment of cancer, wherein the agent has an activity on the cell cycle regulation of tumor cells. For instance, this activity is observed as an action against the pathway involving cyclins; preferably the antiviral agent interferes with cyclin A in the tumor cells. The antiviral agents capable of interfering with the cyclins' pathway are advantageously selected among those which reply to one or several of any of the characteristics which are disclosed in the present patent application.

[0044] In a preferred embodiment of the invention, the antiviral agent which is used is a nucleoside analogue and in a particular embodiment, it is an acyclic nucleoside phosphonate analogue.

[0045] According to a preferred embodiment, the acyclic analogues of nucleosides are substituted-N-alkyl derivatives of heterocyclic basis, in which the nucleoside sugar moiety is replaced by a substituted carbon chain bearing hydroxy groups. Once administered to an organism, the biologically active nucleoside analogues usually modify and give rise to production of 5' monophosphates, active in vivo.

[0046] Preferred antiviral agents concerned by the invention are acyclic nucleoside phosphonate analogues. It is pointed out that said acyclic nucleoside phophonate analogues, are characterized in that their predominant activity is due to DNA polymerase inhibition. Advantageously, in accordance with the invention, they are not dependent upon the presence of a viral tyrosine kinase for their activity. A number of these nucleotide analogues have been synthesized and evaluated both in vitro and in vivo. Examples of these are the [3-hydroxy-2-phosphonylmethoxyprop- yl] derivatives of adenine (HPMPA) or cytosine (HPMPC, cidofovir), cyclic HPMPC (cHPMPC), 9-(2-[phosphonylmethoxyethyl) derivatives of adenine (PMEA, adefovir) or guanine (PMEG), 2-6 diaminopurine (PMEDAP), cyclo-propyl PMEDAP (cPr-PMEDAP) and related compounds with similar activities (29).

[0047] The inventors have obtained particularly interesting results in using HPMPC [(S)-1-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine] (designated Cidofovir.RTM.). This antiviral agent has been extensively disclosed in European patent 0 253 412.

[0048] These anti-viral agents have a predominant mode of action that is targeted at viral and cellular DNA. Their activity is mainly directed to the viral DNA, although not selectively since they have also cellular effects leading to cytotoxicity, especially at concentrations much higher than those needed for the viral inhibition.

[0049] One of the predominant mechanisms involved in the anti-viral effect of the nucleoside phosphonate analogues is the inhibition of the viral DNA polymerase, at a

concentration generally 10 to 1000 lower than that needed to inhibit the cellular DNA polymerases alpha, beta, delta and hence cellular proliferation (28,29).

[0050] The inventors have also shown that the enhanced tumor radiosensitivity observed when combining the administration of radiotherapy with a treatment with an antiviral agent can be associated in several human virus-related cancers, with a down regulation of some viral oncoproteins and with an increase of radiation-induced apoptosis.

[0051] The above disclosed elements relating to the biological pathways explaining the antiviral activity, shall not be construed as providing limitation regarding the activity which is required especially to enable the interaction of the antiviral agent, with the virus or with the host cells. To the contrary, any antiviral agent showing an activity in the treatment of cancer through another biological pathway could be used, provided a result is obtained in cancer treatment.

[0052] In a particular and preferred embodiment, the antiviral agent of the invention is used in combination with an anticancer agent comprising administration of radiotherapy. The antiviral agent is advantageously Cidofovir used in combination with a treatment of radiotherapy.

[0053] The inventors have indeed observed that the association of an antiviral agent and of radiation therapy against tumors including against virus-associated tumors or non virus-associated tumors, enables a synergic effect to occur thereby remarkably improving the likelyhood of success of treatment and moreover enabling the antiviral agent to be used in accordance with treatment modalities which were presented in the prior art as unacceptable for the systemic route of cancer treatment.

[0054] As a matter of fact, the inventors have shown that doses of antiviral agents which are lower than doses which were assayed in the prior art to try to obtain a therapeutic effect, can be used in accordance with the invention, enabling to obtain an unexpected effect with respect to the result which would have been obtained, in cumulating the effects of the individual administration of the antiviral agent with the same dose on the one hand or of the anticancer agent on the other hand.

[0055] Therefore, antiviral agents which would have been disregarded for the treatment of cancer especially by the systemic route of treatment, because the doses which would have been required to obtain a therapeutic effect was not admissible in terms of toxicity, in view of the results disclosed in the prior art have been shown to present an interest in accordance with the present invention, when used in combination with another anticancer agent.

[0056] Especially the combined use of these antiviral agents with anticancer agents such as radiation, provides an effect on tumors or on malignant cells, resulting from cooperation of both agents and in the absence of occurrence of toxic effects, thereby becoming suitable agents for the treatment of cancer, either of virus-associated cancer or of virus-associated cancer.

[0057] The synergic effect has especially been shown on tumors which presented poor reactions when treated by radiation only, or by the antiviral agent alone, including when intratumoral administration of the antiviral agents had no effect or a poor effect on the tumor growth.

[0058] The inventors have shown to the contrary that the combination of the antiviral agent and of radiation induces or enables a significant effect on the growth of the tumor, even enabling the complete remission of the tumor for a period of time over fourty days.

[0059] This effect has been shown in the context of the invention, either after intratumoral administration of the antiviral agent or after subcutaneous administration of said agent. In this latter case, the doses which can be administered were lower than doses which were disclosed in the prior art, as toxic for the organism.

[0060] In order to illustrate the possible conditions for the treatment, it is

indicated that for an anticancer agent that would be radiotherapy doses comprised within the range of 40 to 70 Gy can be used and for an antiviral agent that would be Cidofovir doses of the order of 1 to 100 mg/kg may be envisaged in human.

[0061] According to another embodiment of the present invention, the antiviral agent is proposed for use in the treatment of cancer, either for the treatment of virus-associated cancer, or for the treatment of non-virus-associated cancer, in combination with an anti-cancer chemotherapeutic agent. This anticancer agent can be chosen in the group of well-known chemotherapeutic agents used in the treatment of cancer, independently of the association of the treated cancer with any virus infection. As an example, cisplatine and etoposide are for instance cited. Treatments involving the use of cytokines are also concerned.

[0062] According to another embodiment, the invention provides for an antiviral agent and its use in the treatment of virus-associated cancer wherein the antiviral agent is used in combination with an anticancer immunotherapeutic agent.

[0063] It is noted that the conventional treatment available for cancer, independently of presence or absence of an associated-virus can be also combined, and especially both radiation, chemotherapeutic and/or immunotherapeutic agents can be used in addition to the treatment by the antiviral agent.

[0064] The antiviral agent which is used according to the invention for the treatment of virus-associated cancer or of non-virus-associated cancer or for the manufacture of a drug for said treatment can be used either through systemic, intratumoral or topical routes, and therefore can be formulated according to the appropriate way depending upon the administration route.

[0065] Parenteral administration is preferred including intravenous, intradermal, intramuscular, intrathecal, and other parenteral administration routes.

[0066] The invention also relates to compositions comprising an antiviral agent which are suitable for administration to the human body comprises the use of antiviral agent at doses which are not toxic for the organism when administered by systemic route and especially which are capable of producing the effect sought. These doses are determined in accordance with the usual practice in this field.

[0067] Such a composition of the invention is appropriate for the treatment of cancer, in particular for the treatment of cancer in a human patient, and in a particular embodiment when combined with the use of another treatment protocol including radiation, chemotherapy and immunotherapy.

[0068] Based on the above given definitions, the invention provides compositions comprising an antiviral agent, said compositions being adapted for use in a treatment of cancer, in combination with anticancer agents.

[0069] Where the antiviral and anticancer agents are both chemotherapeutic substances, they may be associated in kits, if appropriate.

[0070] Other features of the invention and advantages of the use of antiviral agents in accordance with the invention are provided in the following examples.

[0071] When a virus is associated with the occurrence of the cancer requiring therapeutic treatment, it can be in particular a target of the treatment as DNA virus.

[0072] Within the group of cancers associated with infection by DNA viruses, the invention relates to the treatment of virus-associated cancers wherein the occurrence of the cancer is linked with the infection by a virus chosen among Herpes viruses, Adenoviruses (21), Polyoma viruses, Papillomaviruses (HPV) (2,3, 4, 9, 10, 20, 22), Epstein-Barr viruses (5, 15,23), Hepatitis DNA viruses (HBV or HCV).

[0073] In the above paragraphs, some specific cancers have been cited which are known to be associated with infection by particular viruses or virus strains.

[0074] The invention especially concerns the use of antiviral agents in the above and following described conditions in the treatment of HPV-associated cancers, EBV-associated cancers or HBV-associated cancers, HCV-associated cancers.

[0075] It is emphasized that the effect which is sought in using antiviral agents for the treatment of virus-associated cancers is not dependent upon the cellular type of the malignant cells or dependent upon the tumor and unexpectedly is efficient even in the absence or virus.

[0076] The invention also relates to the association, for example in a kit, of an antiviral agent and of an anticancer agent.

[0077] Said antiviral agent and said anticancer agent can be used, depending upon their nature, either together, including in the same composition for administration to the patient, or can be physically separated for simultaneous or concomitant use. Alternatively, the antiviral agent and the anticancer agent can be used sequentially during the administration of the treatment.

LEGEND TO FIGURES

[0078] FIG. 1 shows the effect of combining the nucleoside phosphonate HPMPC (Cidofovir), and irradiation on clonogenic cell survival in 3 human cancer cell lines. The effect of the cidofovir alone was substracted for each point measurement. The increased cell kill obtained by the combined treatment was observed both for the virus-related (Raji and HTB33) and for the non-virus-related cancer cells (HTB31).

[0079] FIG. 2 shows the effect of the combination of intra-tumor injection of cidofovir and irradiation on tumor growth of several human xenograft cancers in nude mice. The effect is expressed as the % of the initial tumor volume as a function time after the treatment (days). For each cell line, a control group was used as well as a group of irradiation alone (IR), irradiation+cidofovir (IR+VIT), and cidofovir alone (VIT). The results show in all cases a major effect on tumor growth in the group combining the 2 agents (HEP2, HTB33, C15, Raji). For the C15 experiments is also shown the effect of sub-cutaneous injection of 50 mg/kg of cidofovir in combination with irradiation (VSC+IR), showing that intra-tumor and subcutaneous administrations of cidofovir induced, in combination with irradiation, an anti-tumor effect of the same magnitude.

[0080] FIG. 3: Proportion of apoptopic cells and LMP-1/Bcl2 expression in EBV+ cells (C15 and RAJI) with and without Cidofovir.

[0081] a, RAJI cells were cultured in the presence of Cidofovir (5 and 10 .mu.g/ml) and irrediated 48 hours later with 3 Gy and then assayed for apoptosis by FACS analysis. C15 tumors were injected intra-tumorally for 5 days with Cidofovir (50 mg/kg/day) and received 7 Gy on day 3 and 5. Animals were sacrified on day 7 and tumors were dissected and prepared for FACS analysis of propidium-iodide nuclei staining as described above.

[0082] b, RAJI cells were cultured in the presence or absence of Ciodofovir (10 .mu.g/ml). At 48 hrs, cells were harvested and analyzed for the expression of LMP1, bcl-2 and bax by Western-blot. For C15, at day 7 portions of tumors where lysed in RIPA buffer and protein extracts were immunoblotted with anti-LMP-1 antibody. The blot from b was stripped and re-probed with a monoclonal .beta.-actin antibody. Comparable results were obtained in 3 independent experiments.

[0083] FIG. 4: Viral oncoproteins (E6/E7) and cellular proteins (p53) expression in HPV+ HTB33 and HEP2 cells, with and without Cidofovir.

[0084] a.sub.2b.sub.2 HEP2 (a) and HTB33 (b) cells were cultured in the presence or absence of Cidofovir (10 .mu.g/ml) for 3 and 6 days, and cells were collected in exponential phase, lysed and total protein were immunoblotted with the Ab-1 anti-E7, C1P5 anti-B6, and DO7 anti-p53. The blots were stripped and re-probed with a monoclonal .beta.-actin antibody.

[0085] Densitometric Analysis of E6 and p53 Bands

[0086] HTB33: E6 band was scored 1 without Cidofovir, 0.67 and 0.32, respectively for 3 and 6 days of Cidofovir exposure. P53 density was scored 1 without Cidofovir, 2.1 and 3.7 respectively for 3 and 6 days of Cidofovir exposure.

[0087] HEP2: E6 band was scored 1 without Cidofovir, 0.7 and 0.25, respectively for 3 and 6 days of Cidofovir exposure. P53 density was scored 1 without Cidofovir, 1.2 and 1.65 respectively for 3 and 6 days of Cidofovir exposure. Comparable results were obtained in 3 independent experiments.

EXAMPLES

[0088] Cell Lines

[0089] A typical EBV+ human nasopharyngeal carcinoma cell line like C15 (30) was used in vivo. An EBV+ lymphoma cell lines (Raji) EBV+ and 2 HPV+ squamous cell carcinoma lines, 1 of which originated from the uterine cervix (HTB33) and 1 from the head and neck (HEP2, HPV18+) were used.

[0090] A panel of 3 human cancer cell lines from the same tissue origin, but lacking the viral infection were also used; namely 2 HPV-squamous carcinoma cells SCC97 (head and neck), HTB31 (cervix) and the EBV-Ramos lymphoma cells.

[0091] Cell lines Raji (CCL-86), Ramos (CRL-1596), Hep2 (CCL-23), C33A (HTB-31) and Me-180 (HTB-33) are available in the ATCC (American Type Culture Collection) catalogue.

[0092] Cells were grown in MEM medium supplemented with 15% fetal calf serum, penicillin/streptomycin and 2 mM glutamine at 5% CO2.

[0093] Apoptosis Assay

[0094] The cell cycle distribution was estimated by staining ethanol-fixed cells with propidium iodide and monitoring by FACScan flow cytometer (Becton Dickinson) using cellQuest software. Briefly, 1.times.10.sup.6 cells were cultured without or with 5 and 10 .mu.g/ml of Cidofovir, 24 hours later cells were irradiated with 3 and 6 Gy and collected 12 and 24 hours after irradiation. The percentage of apoptotic cells was determined by sub-G1 peak.

[0095] Histological Sections

[0096] At 10 day after treatment, mice with HPV+ tumors from all groups were sacrified and tumors were excised and fixed in 10% neutral buffered formalin (NBF). The sections from each group were heamatoxylin and eosin (H&E)-stained for histological analysis.

[0097] Immunoblot Analysis

[0098] To prepare total proteins, cells lysates were extracted with lysis buffer 50 mM tris, pH 8, 120 mM NaCl, 0,1% SDS, and 0,5% NP-40. The protein concentration in the soluble fraction was determined by using a BioRad protein assay reagent. The viral oncoprotein LMP1 was detected by immunoblotting with a monoclonal anti-LMP1 antibody (clone CS1,CS2,CS3 & CS4 cocktail, RDI). The following antibodies were used: anti-Bcl2 (clone 100 Santa Cruz Biotechnology), anti-Bax (clone B-9, Santa Cruz, anti-E6 (clone CIP5, abcam), anti-E7 (clone Ab-1, oncogène), anti-p53 (clone DO7, Dako). Anti .beta.-actin (clone AC-40, Sigma) was used to control protein loading. Autoradiograms of the Western blot were scanned with the Gil doc 1000 image scanner (Bio-rad, Hercules, Calif.) and densitometric analysis of the bands was performed using the molecular analyst software program (Bio-rad, Hercules, Calif.).

[0099] Statistical Analysis

[0100] In vivo data are reported as the percentage of original (day 0) tumor volume and plotted as fractional tumor volume.+-.S.E. Statistical significance was determined by Kruskal/Wallis and Mann-Withney U tests.

[0101] In vivo Experiments

[0102] Female Swiss nu/nu mice were housed throughout experiments in sterile isolators and fed ad libitum with irradiated food (UAR, Villemoisson/Orge, France) and filtered water. Experiments were performed according to the regulation n.degree.86/609/CEE of the European Community. Cell lines were established in vivo in Swiss athymic mice by subcutaneous injection in the right flank of 5.times.10.sup.6 cells per animal and subsequently maintained in vivo by sequential passages in animals aged 6 to 8 weeks. Nude mice bearing 500-1000 mm3 tumors were used for in vivo experiments. Two types of control were used including both injection of PBS (intra-tumor and intravenous (IV)), irradiation alone, or chemotherapy alone.

[0103] Irradiation and Clonogenic Survival Assay.

[0104] Irradiation of cells was performed using a .sup.137Cs .gamma.-rays source at a dose rate of 1.45 Gy.min.sup.-1. Briefly survival curves were obtained by irradiating cells (0 to 6 Gy). The linear-quadratic model was used for fitting survival curves. Quantification of radiosensitivity was obtained by the surviving fraction at 2 Gy (SF2). Cell survival was also assessed by using proliferation tests (incorporation of tritiated thymidine and MTT). Irradiation of animals was performed using a 200 kv apparatus.

[0105] Molecular Basis of the Invention

[0106] This aspect was mainly studied using western immunoblots and flow cytometry (FACS) for protein expression analysis and protein co-precipitation analysis (immunoprecipitation).

[0107] The Combination of Cidofovir and Ionizing Radiation Increases Apoptosis and Tumor Necrosis.

[0108] Cidofovir is a potent inhibitor of the replication of EBV and HPV in cell culture. In addition, the incorporation into the cellular DNA of the infected cell may disrupt the genomic integrity and enhance susceptibility to apoptosis or necrosis. In C15 and RAJI cell lines, Cidofovir (10 .mu.g/ml) combined with irradiation (3 and 6 Gy) induced a marked increase of apoptosis (FIG. 3a). The histological sections showed that increased tumor necrosis was predominantly seen in the 2 HPV+ models (data not shown). Both in EBV and HPV cancer cells, no significant change in radiation-induced DNA repair was observed, as measured at the chromosomal level by Fluorescence In Situ Hybridization (FISH) (data not shown).

[0109] Cidofovir Induces a Modulation of Some Viral Oncoproteins.

[0110] The effect of the combined treatment was major in the EBV+ and HPV+ cancer cells, whereas it was relatively marginal in the corresponding virus negative models, suggesting a potential role for some viral oncoproteins in this process (FIG. 1). Indeed, the transforming properties of the EBV and HPVs are attributed to the interaction of viral oncoproteins with critical cellular proteins that control cell proliferation and apoptosis cell death (31,32). Gene-transfer experiments have shown that the expression of LMP-1 specifically inhibits p53-mediated apoptosis, by inducing the antiapoptotic cellular genes, Bcl-2 and A20.

[0111] Cidofovir exposure was able to induce a marked decrease of LMP-1 expression both in RAJI and C15 cells (FIG. 3b). We observed significant inhibition of LMP-1 expression as early as 24 hours (data not shown) and more pronounced inhibition 48 hours after exposure to Cidofovir (FIG. 3b). The result might be related to the inhibition of the viral replication and it is compatible with the short half-life of LMP-1 protein (33). Importantly, the inhibition of LMP-1 was associated with a downregulation of the LMP-1 inducible gene Bcl2, an up-regulation of the pro-apoptotic Bax expression (FIG. 3b). In latent EBV infection as it occurs in C15 an RAJI cells, the induction of antiapoptotic genes by LMP-1 presumably contributes to protect cells from apoptosis (31). Such a down regulation of LMP-1 and Bcl2 by Cidofovir could explain the enhancement of the sensitivity to readiation-induced

apoptosis observed in the FBV+ cell lines (RAJI and C15). Downregulation of LMP-1 is reported here for the first time in cancer cells using a pharmacological approach.

[0112] E6 and E7 oncoproteins are involved in cellular transformation by interacting with the tumor suppressor proteins Rb and p53, respectively (34, 35). P53 functional assay in yeast (36) showed that p53 gene was wild type in cervical carcinoma HTB33 and head and neck HEP2 cells (data not shown). However, the basal level of p53 expression was relatively low as shown in FIG. 4a, and a previously reported (35) which is compatible with a proteasome-mediated degradation of p53 by E6 oncoprotein expressed in these two cell lines. Unlike other cancers in which p53 is mutated, the notion has arisen that the effect of E6 with respect to p53 is equivalent to an inactivating mutation of p53 (32). This underlines the importance of targeting E6 for therapeutic intervention since blocking E6-mediated degradation of p53 may be efficient to restore a normal p53 expression in HPV1 cells (32). In this study, we showed that Cidofovir exposure was able to down-regulate E6 expression with subsequent increase of p53 expression (FIG. 4a, 4b). This phenomenon was likely to enhance the sensitivity to ionising radiation since the restoration of a normal wtp53 expression has been shown to increase the radiosensitivity in many human carcinoma models (37,38). In addition, a decreased expression of the viral oncoprotein E7 was observed when these HPV+ cells were exposed to Cidofovir (FIG. 4b). It is important to point out that Cidofovir was able to influence both E6 and E7 expression which may be more efficient for growth suppression than targeting each of these proteins separately (39).

[0113] Conversely, recent data have shown that E6/E7 viral oncoproteins overexpression was associated to p53 downregulation and radiation induced apoptosis inhibition in cervical carcinoma cell line (40).

[0114] Some Examples of Interaction Between the Acyclic Nucleoside Phosphonate Analogues and Cytotoxic Agents are Presented Herewith:

Example N.degree.1

Combination of an Acyclic Nucleoside Phosphonate Analogue with Irradiation in Human Cancer Cells in vitro

[0115] The example presented herewith relates to the combination of cidofovir with irradiation, which was evaluated in vitro in various virus-related and non virus-related human cancers.

[0116] It was studied in EBV+ human carcinoma C15 cells, EBV+ lymphoma Raji cells, 2 HPV+ carcinoma HTB33 and HEP2 cells. The effect of the combination was also studied in 3 human cell lines lacking the viral infection namely Ramos (lymphoma) HTB31 and SCC97 (carcinoma) cells.

[0117] For each cell line, several concentrations of cidofovir were used in vitro in combination with irradiation (between 1 and 10 .mu.g/ml). The effect of the combined treatment was evaluated using both a proliferation test and a clonogenic assay for cell survival. These two methods gave convergent results showing in all the EBV+ and HPV+ cell lines, that the addition of cidofovir to irradiation produced a pronounced radiosensitization as shown by the dramatic decrease of the SF2 (surviving fraction at 2 Gy). This marked radiosensitizing effect was not restricted to the cell lines exhibiting a viral infection since non virus-containing cells Ramos, HTB31, and SCC97 were also markedly radiosensitized by the cidofovir (see examples in FIG. 1).

Example N.degree.2

Combination of an Acyclic Nucleoside Phosphonate Analogue with Irradiation in Human Cancer Xenografts in vivo

[0118] The example presented herewith also relates to the combination of cidofovir with irradiation which was evaluated in vivo in various human viral-associated and also in non viral associated human cancers. The effect of cidofovir alone or combined with irradiation was studied in vivo in nude mice bearing 500-1000 mm3 tumor xenografts. The treatment consisted of 60 mg/kg daily of cidofovir intra-tumor

injection for 5 days. In the combined group, irradiation (7 Gy) was performed on day 3 and 5 of cidofovir. As shown in FIG. 2; both irradiation alone and cidofovir alone induced a weak growth delay, whereas the concomitant association of both agents dramatically reduced the growth delay for the virus-positive tumors (C15, Raji, HEP2, HTB33 . . .), as well as for the non-virally induced tumors tested. In all cases, in the group receiving the combined treatment, nearly all the tumors were found to be in complete remission, 30 to 40 days after the treatment, suggesting the existence of a major interaction between the 2 agents.

[0119] Effect of the Route of Administration in vivo:

[0120] In vivo, the effect of non toxic doses 25 to 75 mg/kg from day 1 to day 5 of the nucleoside phosphonate analogues administered intra-peritoneally or subcutaneously (C15, HTB33 etc . . .) was found to be as efficient for tumor inhibition (FIG. 2), as compared to the intra-tumor mode of administration. The doses used intra-peritoneally and subcutaneously were in the range of 0.5 to 1.66 times the doses used for intra-tumor injections.

[0121] Molecular Basis of the Observed Effect

[0122] The molecular basis of the interaction is not fully understood. In the non-virus related cancer types, nucleoside phosphonate analogue were found to interfere with DNA repair, apoptosis and cell cycle regulation (cyclin D1, E and A), which could explain the observed radiosensitization. In addition to these mechanisms, in the virus-associated cancer types, an inhibition of the viral oncoproteins could be also observed. For example, in the EBV+ raji cells, nucleoside phosphonate analogues induced a down regulation of the viral oncoprotein LMP1 and consequently the anti-apoptotic Bcl2 gene expression was down regulated, contributing to increase radio-induced tumor cell kill.

[0123] In conclusion, the combination of an anti-viral nucleoside phosphate analogue and irradiation described in this example represents a totally new approach for the treatment of virus-associated and non-virus-associated human cancers. Indeed, the results obtained showed a major effect of combining this type of anti-viral agent with irradiation.

Example N.degree.3

Combination of an Acyclic Nucleoside Phosphonate Analogue with Chemotherapeutic Agents in Human Cancer Cells

[0124] Similar experiments combining a nucleoside analogue with cytotoxic agents other than irradiation were performed (chemotherapeutic drugs, cytokines). The example presented herewith relates to the combination of cidofovir with chemotherapeutic drugs which was evaluated in vitro and in vivo in various virus-associated and non virus-associated human cancers. Two drugs were tested, showing a synergic inhibitory effect on tumor cell growth using a combination of a nucleoside phosphonate analogue with cis platinum (2.5 .mu.g/ml, in vitro) and VP16 (5 .mu.g/ml, vitro).

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CLAIMS:

1. An antiviral agent for use in combination with an anticancer agent, for the treatment of cancer.

2. Use of an antiviral agent for the manufacture of a drug for the treatment of cancer, wherein said drug is used in a combined treatment with an anticancer agent.

3. Use of an antiviral agent for the manufacture of a drug suitable for the treatment of cancer by systemic route.

4. Antiviral agent or its use according to anyone of claims 1 to 3, wherein the cancer is a virus-associated cancer.

5. Antiviral agent or its use according to anyone of claims 1 to 3, wherein the cancer is a non-virus-associated cancer.

6. Kit of parts comprising an antiviral agent and an anticancer agent, for combined or separate use.

7. An antiviral agent, its use or a kit comprising an antiviral agent, according to anyone of claims 1 to 6, wherein the antiviral agent is virus non-specific.

8. An antiviral agent, its use or a kit comprising an antiviral agent, according to anyone of claims 1 to 7, wherein the antiviral agent has a broad-spectrum antiviral activity.

9. An antiviral agent, its use or a kit comprising an antiviral agent, according to anyone of claims 1 to 8, wherein the antiviral agent has a cytotoxic activity.

10. An antiviral agent, its use or a kit comprising an antiviral agent, according to anyone of claims 1 to 9, wherein the antiviral agent has an inhibition activity against viral and/or cellular polymerases.

11. An antiviral agent, its use or a kit comprising an antiviral agent, according to anyone of claims 1 to 9, wherein the antiviral agent is a nucleoside phosphonate analogue.

12. An antiviral agent, its use or a kit comprising an antiviral agent, according to anyone of claims 1 to 11, wherein the antiviral agent is an acyclic nucleoside phosphonate analogue.

13. An antiviral agent, its use or a kit comprising an antiviral agent, according to claim 11, wherein the antiviral agent is HPMPC [(S)-1-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine].

14. An antiviral agent, its use or a kit comprising an antiviral agent, according to anyone of claims 1 to 9, wherein said antiviral agent has an activity against cell cycle regulation, especially through cyclins.

15. An antiviral agent, its use or a kit comprising an antiviral agent according to

anyone of claims 1 to 14, wherein the antiviral agent is active against cyclins.

16. An antiviral agent, its use or a kit comprising an antiviral agent according to anyone of claims 1 to 14, for use in combination with anticancer radiotherapy.

17. An antiviral agent, its use or a kit comprising an antiviral agent according to anyone of claims 1 to 14, for use in combination with an anticancer chemotherapeutic agent.

18. An antiviral agent, its use or a kit comprising an antiviral agent according to anyone of claims 1 to 14, for use in combination with an anticancer immunotherapeutic agent.

19. An antiviral agent, its use or a kit comprising antiviral agent according to claim 18, wherein the immunotherapeutic agent is associated with a cytokin.

20. An antiviral agent, its use or a kit comprising an antiviral agent according to anyone of claims 1 to 14, for use in combination with at least two anticancer agents chosen among radiation, chemotherapeutic and immunotherapeutic agents.

21. An antiviral agent, its use or a kit comprising an antiviral agent according to anyone of claims 1-20 for the manufacture of a drug for systemic treatment of virus-associated cancer in human.

22. An antiviral agent, its use or a kit comprising an antiviral agent according to anyone of claims 1 to 20, for the manufacture of a drug for systemic treatment of non-virus-associated cancer in human.

23. An antiviral agent, its use or a kit comprising an antiviral agent according to anyone of claims 1 to 20, for the manufacture of a drug for intratumoral treatment of cancer in human.

24. An antiviral agent, its use or a kit comprising an antiviral agent according to claim 23, for the systemic treatment of cancer in human.

25. Use according to anyone of claims 1 to 20 or composition according to anyone of claims 21 to 23, wherein the antiviral agent is HPMPC and the other anticancer therapeutic agent is radiotherapy.

26. An antiviral agent, a composition or a use according to anyone of claims 23 to 25, for the treatment of a virus-associated cancer.

27. An antiviral agent, a composition or a use according to anyone of claims 23 to 25, for the treatment of a non virus-associated cancer.

28. Antiviral agent or its use according to anyone of claims 4, 6 to 20 or composition according to anyone of claims 21 to 24 wherein the viral-associated cancer is associated with an infection by a virus chosen among herpes-, adeno-, polyoma-, papilloma-, Epstein-Barr or Hepatitis DNA viruses.

29. Antiviral agent or its use according to anyone of claims 4, 6 to 20, wherein the cancer is a virus-associated cancer involving infection by EBV or HPV virus.

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L1β: Entry 13 of 34 File: PGPB Apr 18, 2002

PGPUB-DOCUMENT-NUMBER: 20020045162
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020045162 A1

TITLE: Identification of viral agents in breast ducts and antiviral therapy therefore

PUBLICATION-DATE: April 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	

US-CL-CURRENT: 435/5; 435/7.1

CLAIMS:

What is claimed is:

1. A method for identifying a patient having an increased risk for developing breast precancer or breast cancer, said method comprising: providing a ductal fluid sample from one duct of a breast of a patient, said fluid not mixed with ductal fluid from any other duct of the breast; and detecting a viral agent in the ductal fluid sample.

2. A method as in claim 1, wherein the viral agent is selected from the group consisting of a whole virus, a portion of a virus, a viral protein, a viral nucleic acid, and a viral marker, in the sample.

3. A method as in claim 1, wherein the ductal fluid is retrieved by nipple aspiration.

4. A method as in claim 1, wherein the ductal fluid is retrieved by placing a ductal access tool in the duct and infusing fluid into the duct through the tool and retrieving from the accessed duct through the tool a portion of the infused fluid mixed with ductal fluid.

5. A method as in claim 3, wherein the method is repeated for more than one duct on a breast.

6. A method as in claim 3, wherein the method is repeated for a plurality of ducts on a breast.

7. A method as in claim 1 further comprising analyzing the ductal fluid for abnormal cytology.

8. A method as in claim 1, wherein a viral agent is detected, further comprising monitoring a variable selected from the group consisting of a viral titer, concentration of a viral agent, and presence of a viral marker by taking repeated periodic ductal fluid samplings.

9. A method as in claim 8, wherein a viral agent is monitored and the viral agent is selected from the group consisting of a whole virus, a portion of a virus, a viral protein, a viral nucleic acid, and a viral marker by taking repeated periodic ductal

fluid samplings.

10. A method as in claim 8, wherein the periodicity is selected from the group consisting of daily, weekly, biweekly, monthly, bimonthly, every six months, annually, and biannually.

11. A method as in claim 1, wherein the viral agent is selected from the group consisting of papilloma virus, epstein-barr virus, and herpes virus.

12. A method of treating a patient at risk for or having a breast precancer or breast cancer comprising: detecting a viral agent in a fluid sample collected from a breast duct; and delivering to the patient a composition comprising an antiviral agent specific for the detected viral agent.

13. A method as in claim 12, wherein the viral agent is selected from the group consisting of a whole virus, a portion of a virus, a viral protein, a viral nucleic acid, and a viral marker.

14. A method as in claim 12, wherein the antiviral agent is delivered intraductally to a duct in which the viral agent is detected.

15. A method as in claim 12, wherein viral agent is detected in more than one fluid sample collected separately from more than one breast duct

16. A method as in claim 12, wherein viral agent is detected in a fluid sample collected from a plurality of breast ducts.

17. A method as in claim 12, wherein the viral agent is selected from the group consisting of papilloma virus, epstein-barr virus, and herpes virus.

18. A method as in claim 12, wherein the antiviral agent is selected from the group consisting of an anti-HPV viral agent, an anti-EBV viral agent, and an anti-herpes viral agent.

19. A method as in claim 12, wherein the composition comprising said antiviral agent is delivered systemically.

20. A method as in claim 14, wherein the antiviral agent is delivered by placing a ductal access tool in a target duct and infusing a composition comprising the antiviral agent into the duct through the tool.

21. A kit or system for identifying a patient having an increased risk for developing breast precancer or breast cancer, said kit or system comprising a ductal access tool, and reagents and instructions for detecting a viral agent in ductal fluid collected using the tool.

22. A kit or system for treating a patient at risk for or having a breast precancer or breast cancer in which a viral agent is a component and is present in the affected duct, said kit or system comprising a ductal access tool for intraductal delivery of a composition, the composition comprising an antiviral agent, and instructions for use.

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L18: Entry 16 of 34 File: PGPB Feb 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020019017
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020019017 A1

TITLE: METHOD AND KIT FOR OBTAINING FLUIDS AND CELLULAR MATERIAL FROM BREAST DUCTS

PUBLICATION-DATE: February 14, 2002

INVENTOR-INFORMATION:

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HUNG, DAVID	BELMONT	CA	US	
HE, XUANMIN	PALO ALTO	CA	US	

US-CL-CURRENT: 435/7.23

CLAIMS:

What is claimed is:

1. A method for obtaining material from a milk duct in a breast of a patient, said method comprising: (a) locating a single milk duct; (b) introducing a washing fluid substantially throughout the duct without rupture; (c) collecting at least a portion of the washing fluid from the duct; and (d) identifying materials in the washing fluid collected from the duct.

2. A method as in claim 1, further comprising obtaining material from at least one additional single milk duct of the same breast by repeating steps (a) through (d) on another single milk duct.

3. A method as in claim 2, wherein the steps are repeated for all ducts in the nipple.

4. A method as in claim 1, wherein the materials identified in the washing fluid include ductal epithelial cells.

5. A method as in claim 4, further comprising examining the morphology of the epithelial cells in the washing fluid to determine if they are atypical in order to assess the likelihood of a cancer present in the cellular lining of the duct.

6. A method as in claim 1, wherein the materials comprise molecular species.

7. A method for obtaining material from a milk duct in a breast of a patient, said method comprising: (a) locating at least one of the ductal orifices on a nipple of the breast; (b) introducing a catheter having at least one lumen through one of the ductal orifices and into the ductal passage; (c) introducing a washing fluid through a lumen into the ductal passage; (d) collecting the washing fluid from the ductal passage through a lumen of the catheter; and (e) identifying materials present in the collected washing fluid.

8. A method as in claim 7, further comprising dilating the ductal orifice prior to introducing the catheter.

9. A method as in claim 7, wherein the catheter includes at least two lumens and washing fluid introducing and collecting steps are performed through separate lumens in the catheter.

10. A method as in claim 9, wherein a preselected volume of the washing fluid is introduced to the duct through one lumen and excess volume flows out of the duct through another catheter lumen.

11. A method as in claim 10, wherein the volume of washing fluid is at least 5 ml.

12. A method as in claim 8, wherein the volume of washing fluid is at least 10 ml.

13. A method as in claim 7, further comprising obtaining and identifying material from at least one additional single milk duct of the same breast by repeating steps (a) through (e) on another single milk duct.

14. A method as in claim 13, wherein the steps are repeated for all ducts in the nipple.

15. A method as in claim 6, wherein the material in the washing fluid include epithelial cells.

16. A method as in claim 15, further comprising examining the morphology of the epithelial cells in the washing fluid to determine if they are atypical in order to assess the likelihood of a cancer present in the cellular lining of the duct.

17. A method as in claim 7, wherein the materials comprise molecular species.

18. A kit for obtaining material from a milk duct of a breast, said kit comprising: a catheter; and instructions setting forth a method for use of the dual-lumen catheter according to claim 7.

19. A method for obtaining fluid and cellular material from a breast duct including fluid and cellular material from distal areas of the ductal architecture of a breast milk duct comprising: (a) introducing washing fluid into a milk duct, (b) applying external pressure to the breast; and (c) collecting at least a portion of the washing fluid from the duct, wherein the portion of the washing fluid collected comprises fluid and cells from the duct.

20. A method as in claim 19, wherein introducing washing fluid comprises introducing a sufficient amount of washing fluid thereby substantially filling the duct.

21. A method as in claim 19, wherein the pressure is applied manually.

22. A method as in claim 19, wherein the pressure is applied mechanically.

23. A method as in claim 19, wherein applying external pressure mixes the fluid and cells together in a duct.

24. A method as in claim 19, wherein the pressure is applied beginning at the base of the breast and moving towards the areola and nipple regions of the breast.

25. A method as in claim 19, wherein introducing a washing fluid comprises continuous or intermittent infusion of washing fluid over a period of time.

26. A method as in claim 19, wherein applying external pressure to the breast comprises applying external pressure periodically, continuously, or cyclically during infusion of the wash fluid.

27. A method for obtaining fluid and cellular material from a breast duct including fluid and cellular material from distal areas of the ductal architecture of a breast milk duct comprising: (a) introducing washing fluid into a milk duct, and providing continuous or intermittent infusion of the wash fluid for a period of time; (b) applying external pressure to the breast and repeating application of external pressure periodically, continuously, or cyclically during infusion of the wash

fluid; and (c) collecting the washing fluid from the duct during the infusion and application of external pressure, wherein the washing fluid collected comprises fluid and cells from the duct.

28. The method of claim 27, wherein the pressure is applied manually or mechanically.

29. A method as in claim 19 or 27, wherein introducing and collecting comprise access of a breast duct by an access tool having at least one lumen

30. The method of claim 28, wherein collecting comprises applying suction to an outflow lumen of a dual lumen catheter to draw fluid out from the duct.

31. A method of obtaining material from a milk duct in a breast of a patient comprising: (a) locating at least one ductal orifice on a nipple of the breast; (b) introducing an access tool having at least one lumen through one of the ductal orifices and into the ductal passage; (c) introducing a washing fluid through a lumen into the ductal passage; (d) applying external pressure to the breast; (e) collecting the washing fluid from the ductal passage through a lumen of the access tool during or after fluid introduction and application of external pressure to the breast; and (f) identifying materials present in the collected washing fluid.

32. The method according to any of claims 19, 27, or 31, wherein the washing fluid comprises a mixture of air and fluid.

33. A kit for obtaining material from a milk duct of a breast comprising: an access tool having at least one lumen, instructions setting forth a procedure according to the method of any of claims 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 31, and a container for the kit contents.

34. A kit as in claim 33, further comprising reagents for washing, collection, preservation or analysis of ductal fluid.

35. A kit for obtaining material from a milk duct of a breast comprising: an access tool having at least one lumen; instructions setting forth a procedure according to the method of claim 29; and a container for the kit contents.

36. A kit for obtaining material from a milk duct of a breast comprising: an access tool having at least one lumen; instructions setting forth a procedure according to the method of claim 30; and a container for the kit contents.

37. A kit for obtaining material from a milk duct of a breast comprising: an access tool having at least one lumen; instructions setting forth a procedure according to the method of claim 32; and a container for the kit contents.

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L18: Entry 21 of 34 File: PGPB Oct 25, 2001

PGPUB-DOCUMENT-NUMBER: 20010034038
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010034038 A1

TITLE: Isolated ductal fluid sample

PUBLICATION-DATE: October 25, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	

US-CL-CURRENT: 435/7.23; 435/6

CLAIMS:

What is claimed is:

1. A method for preparing a sample for use in diagnosis of breast cancer or pre-cancer comprising: isolating a ductal fluid sample from one duct of a breast of a patient, said isolated ductal fluid not mixed with ductal fluid from any other duct of the breast.

2. A method as in claim 1, further comprising: examining the isolated ductal fluid sample to determine the presence or absence of a marker.

3. A method as in claim 1, wherein the duct from which the ductal fluid is isolated is not spontaneously discharging ductal fluid.

4. A method as in claim 2, wherein the marker is selected from the group consisting of: lysophosphatidic acid, a lysophospholipid, paladin, a portion of palladin, a nucleic acid encoding a polypeptide comprising at least a portion of paladin, Lg, a portion of Lg, a nucleic acid encoding a polypeptide comprising at least a portion of Lg, E2F1, a portion of E2F1, a nucleic acid encoding a polypeptide comprising at least a portion of E2F1, T1A12/mac 25, a portion of T1A12/mac 25, a nucleic acid encoding a polypeptide comprising at least a portion of T1A12/mac 25, MAGUK/ZO-1, a portion of MAGUK/ZO-1, a nucleic acid encoding a polypeptide comprising at least a portion of MAGUK/ZO-1, repressor of estrogen receptor activity (REA), a portion of REA, a nucleic acid encoding a polypeptide comprising at least a portion of REA, prothymosin alpha (PTA), a portion of PTA, a nucleic acid encoding a polypeptide comprising at least a portion of PTA, c-raf kinase, a portion of c-raf kinase, a nucleic acid encoding a polypeptide comprising at least a portion of c-raf kinase, CD66a, a portion of CD66a, a nucleic acid encoding a polypeptide comprising at least a portion of CD66a, KL-1, a portion of KL-1, a nucleic acid encoding a polypeptide comprising at least a portion of KL-1, cell adhesion molecule 5.2 (CAM 5.2), a portion of CAM 5.2, a nucleic acid encoding a polypeptide comprising at least a portion of CAM 5.2, leptin, a portion of leptin, a nucleic acid encoding a polypeptide comprising at least a portion of leptin, Bcl-2 gene product, at least a portion of Bcl-2 gene product or polypeptide, a nucleic acid encoding a polypeptide encoding at least a portion of Bcl-2 gene product, nuclear matrix 23(nm23), a portion of nm23, a nucleic acid encoding a polypeptide comprising at least a portion of nm23, an apotosis-related protein, a portion of said protein, a nucleic acid encoding a polypeptide comprising at least a portion of the apoptosis-related protein, lipocalin NGAL, a portion of lipocalin NGAL, a nucleic acid encoding a

polypeptide comprising at least a portion of lipocalin NGAL, complement regulatory protein CD 46, a portion of CD46, a nucleic acid encoding at least a portion of CD46, complement regulatory protein CD 59, a portion of CD59, a nucleic acid encoding at least a portion of CD59, a nucleic acid encoding a portion of an FHIT gene, loss of heterozygosity at an FRA3B site, MRP-1/CD9, a portion of MRP-1/CD9, a nucleic acid encoding at least a portion of MRP-1/CD9, KAI1/CD82, a portion of KAI1/CD82, a nucleic acid encoding at least a portion of KAI1/CD82, a Fibroblast Growth Factor (FGF), a portion of FGF, a nucleic acid encoding a polypeptide comprising at least a portion of an FGF, Vascular Epithelial Growth Factor (VEGF), at least a portion of VEGF, a nucleic acid encoding at least a portion of VEGF, Insulin-like Growth Factor -1 (IGF-1), at least a portion of IGF1, a nucleic acid encoding at least a portion of IGF-1, tumor amplified kinase STK15 (also BTAK and aurora2), at least a portion of STK15, a nucleic acid encoding a polypeptide comprising at least a portion of STK15, TMS-1, a portion of TMS-1, a nucleic acid encoding a polypeptide comprising at least a portion of TMS-1, maspin, at least a portion of maspin, a nucleic acid encoding a polypeptide comprising at least a portion of maspin, at least a portion of breast cancer associated (BRCA) gene, and at least a portion of a BRCA gene product; CDw60 protein, a portion of CDw60 protein or polypeptide, a nucleic acid encoding at least a portion of a CDw60 protein or polypeptide, mammary expressed enzymes including cytochrome P450s, catechol-O-methyltransferase, epoxide hydrolase, peroxidases, glutathione S-transferases, Nacetyltransferases, or sulfotransferases, a nucleic acid encoding at least a portion of a mammary expressed enzyme, Kallikrein 6 (zyme/protease M/neurosin) protein or polypeptide (hK6), a nucleic acid encoding at least a portion of an hK6 protein or polypeptide; and mammastatin protein or polypeptide, a nucleic acid encoding at least a portion of a mammastatin protein or polypeptide.

5. A method as in claim 1, further comprising: examining the isolated ductal fluid to determine absorption of a molecule by abnormal cells in the fluid.

6. A method as in claim 5, wherein the molecule comprises iodide.

7. A method as in claim 1, further comprising: examining the isolated ductal fluid for a loss of heterozygozity.

8. A method as in claim 1, further comprising examining the isolated ductal fluid for the presence of two or more markers.

9. A method as in claim 1, further comprising examining the isolated ductal fluid for the absence of two or more markers.

10. A method as in claim 1, further comprising examining the ductal fluid for the presence of at least one marker and the absence of at least one marker.

11. A method as in claim 1, further comprising analyzing collected ductal epithelial cells by cytology.

12. A method as in claim 9, wherein the markers are selected from the group consisting of DNA content, p53 gene or gene product, and G-actin or a nucleic acid encoding a polypeptide comprising at least a portion of G-actin.

13. An isolated ductal fluid sample collected from a breast duct in a breast, said isolated ductal fluid not mixed with ductal fluid from any other breast duct.

14. An isolated ductal fluid sample as in claim 13, wherein the sample comprises a marker for analysis.

15. An isolated ductal fluid sample as in claim 14, wherein the analysis comprises determining the presence or absence of the marker.

16. An isolated ductal fluid sample as in claim 13, a portion of said isolated ductal fluid not spontaneously discharging from the breast duct.

17. An isolated ductal fluid sample as in claim 13, wherein the sample comprises 10 or more ductal epithelial cells.

18. An isolated ductal fluid sample as in claim 13, wherein the sample comprises at least one ductal epithelial cells clump.

19. An isolated ductal fluid sample as in claim 18, wherein the clump comprises 5 or more ductal epithelial cells.

20. A method for analyzing breast markers or epithelial cells, comprising: determining the presence or absence of a marker in an isolated ductal fluid sample collected from a breast duct in a breast, said isolated ductal fluid not mixed with ductal fluid from any other breast duct.

21. A method as in claim 20, wherein the duct from which the ductal fluid is isolated is not spontaneously discharging ductal fluid.

22. A method as in claim 20, wherein the marker is selected from the group consisting of: lysophosphatidic acid, a lysophospholipid, paladin, a portion of palladin, a nucleic acid encoding a polypeptide comprising at least a portion of paladin, Lg, a portion of Lg, a nucleic acid encoding a polypeptide comprising at least a portion of Lg, E2F1, a portion of E2F1, a nucleic acid encoding a polypeptide comprising at least a portion of E2F1, T1A12/mac 25, a portion of T1A12/mac 25, a nucleic acid encoding a polypeptide comprising at least a portion of T1A12/mac 25, MAGUK/ZO-1, a portion of MAGUK/ZO-1, a nucleic acid encoding a polypeptide comprising at least a portion of MAGUK/ZO-1, repressor of estrogen receptor activity (REA), a portion of REA, a nucleic acid encoding a polypeptide comprising at least a portion of REA, prothymosin alpha (PTA), a portion of PTA, a nucleic acid encoding a polypeptide comprising at least a portion of PTA, c-raf kinase, a portion of c-raf kinase, a nucleic acid encoding a polypeptide comprising at least a portion of c-raf kinase, CD66a, a portion of CD66a, a nucleic acid encoding a polypeptide comprising at least a portion of CD66a, KL-1, a portion of KL-1, a nucleic acid encoding a polypeptide comprising at least a portion of KL-1, cell adhesion molecule 5.2 (CAM 5.2), a portion of CAM 5.2, a nucleic acid encoding a polypeptide comprising at least a portion of CAM 5.2, leptin, a portion of leptin, a nucleic acid encoding a polypeptide comprising at least a portion of leptin, Bc1-2 gene product, at least a portion of Bcl-2 gene product or polypeptide, a nucleic acid encoding a polypeptide encoding at least a portion of Bcl-2 gene product, nuclear matrix 23(nm23), a portion of nm23, a nucleic acid encoding a polypeptide comprising at least a portion of nm23, an apotosis-related protein, a portion of said protein, a nucleic acid encoding a polypeptide comprising at least a portion of the apoptosis-related protein, lipocalin NGAL, a portion of lipocalin NGAL, a nucleic acid encoding a polypeptide comprising at least a portion of lipocalin NGAL, complement regulatory protein CD 46, a portion of CD46, a nucleic acid encoding at least a portion of CD46, complement regulatory protein CD 59, a portion of CD59, a nucleic acid encoding at least a portion of CD59, a nucleic acid encoding a portion of an FHIT gene, loss of heterozygosity at an FRA3B site, MRP-1/CD9, a portion of MRP-1/CD9, a nucleic acid encoding at least a portion of MRP-1/CD9, KAI1/CD82, a portion of KAI1/CD82, a nucleic acid encoding at least a portion of KAI1/CD82, a Fibroblast Growth Factor (FGF), a portion of FGF, a nucleic acid encoding a polypeptide comprising at least a portion of an FGF, Vascular Epithelial Growth Factor (VEGF), at least a portion of VEGF, a nucleic acid encoding at least a portion of VEGF, Insulin-like Growth Factor -1 (IGF-1), at least a portion of IGF-1, a nucleic acid encoding at least a portion of IGF-1, tumor amplified kinase STK15 (also BTAK and aurora2), at least a portion of STK15, a nucleic acid encoding a polypeptide comprising at least a portion of STKI 5, TMS-1, a portion of TMS-1, a nucleic acid encoding a polypeptide comprising at least a portion of TMS-1, maspin, at least a portion of maspin, a nucleic acid encoding a polypeptide comprising at least a portion of maspin, at least a portion of breast cancer associated (BRCA) gene, and at least a portion of a BRCA gene product; CDw60 protein, aportion of CDw60 protein or polypeptide, a nucleic acid encoding at least a portion of a CDw60 protein or polypeptide, mammary expressed enzymes including cytochrome P450s, catechol-O-methyltransferase, epoxide hydrolase, peroxidases, glutathione S-transferases, Nacetyltransferases, or sulfotransferases, a nucleic acid encoding at least a portion of a mammary expressed enzyme, Kallikrein 6 (zyme/protease M/neurosin) protein or polypeptide (hK6), a nucleic acid encoding at least a portion of an hK6 protein or polypeptide; and mammastatin protein or polypeptide, a nucleic

acid encoding at least a portion of a mammastatin protein or polypeptide.

23. A method as in claim 20, wherein the marker is absorption of a molecule by abnormal cells in the fluid.

24. A method as in claim 23, wherein the molecule comprises iodide.

25. A method as in claim 20, wherein the marker is a loss of heterozygozity.

26. A method as in claim 20, wherein the presence of two or more markers is determined.

27. A method as in claim 20, wherein the absence of two or more markers is determined.

28. A method as in claim 20 wherein the presence of at least one marker and the absence of at least one marker is determined.

29. A method as in claim 20 wherein the marker determined is cytology of ductal epithelial cells.

30. A method as in claim 20, wherein the marker is selected from the group consisting of DNA content, p53 gene or gene product, and G-actin or a nucleic acid encoding a polypeptide comprising at least a portion of G-actin.

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L18: Entry 34 of 34 File: USPT Sep 1, 1981

US-PAT-NO: 4286571
DOCUMENT-IDENTIFIER: US 4286571 A

TITLE: Kenshin heating instrument

DATE-ISSUED: September 1, 1981

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hung; David P. J.	Bayside	NY	11364	

US-CL-CURRENT: 126/206

CLAIMS:

What is claimed is:

1. A hand-held, non-electrically powered heating instrument, comprising:

a generally cylindrical, hollow, elongated, metallic first element having means for mounting a charge of burnable fuel therein and also having a plurality of air vents at one end thereof and an air inlet opening at the opposite end thereof;

a generally cylindrical, hollow, elongated, metallic second element having a substantially closed end and an opposite open end and a plurality of air vents formed substantially adjacent to said closed end thereof, said second element being configured and dimensioned to permit said first element to be releasably and telescopically received therein through said open end thereof, so that said air vents of both elements may communicate with one another, said first and second elements being slidable relative to one another in both a rotatable and longitudinal manner so as to permit regulation of the amount of air flowing through said air inlet opening and through said vents.

2. The heating instrument according to claim 1, additionally including a charge of burnable fuel.

3. The heating instrument according to claim 2, wherein said charge comprises a stick of incense.

4. The heating instrument according to claim 1, wherein said first element has a knob-like end segment formed on said opposite end thereof in which said air inlet opening is formed which serves as a finger grip to permit facile sliding movement of said first element relative to said second element.

5. The heating element according to claim 4, wherein said first element has a pair of opposed radially outwardly-extending resilient flanges disposed adjacent to said one end thereof which serve to enhance frictional engagement between said first and second elements during telescopic engagement therebetween.

6. The heating element according to claim 1, wherein said plurality of air vents formed in said second element comprises a plurality of parallel and radially spaced-apart elongated slots formed in said second element adjacent to said closed end thereof and wherein said closed end has an air outlet opening

extending therethrough.

7. The heating element according to claim 1, wherein said first element has an opening extending through said one end thereof which serves as said mounting means and in which said charge of fuel may be mounted.

8. The heating element according to claim 5, wherein said plurality of air vents of said first element comprise a plurality of parallel and radially spaced-apart elongated slots formed in said first element on the opposite lateral sides of said flanges.

9. The heating element according to claim 1, wherein said elements are made from silver-coated brass.

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L18: Entry 29 of 34 File: USPT May 11, 1999

US-PAT-NO: 5902582
DOCUMENT-IDENTIFIER: US 5902582 A

TITLE: Use of TFPI inhibitor for treatment of cancer

DATE-ISSUED: May 11, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hung; David T.	San Francisco	CA		

US-CL-CURRENT: 424/130.1; 514/12

CLAIMS:

What is claimed is:

1. A method of inducing or augmenting tissue factor expression or release in a tumorous tissue in an individual comprising administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of an inhibitor of tissue factor pathway inhibitor (TFPI).

2. The method of claim 1, wherein induction or augmentation of tissue factor expression or release is initiated by radiation, cryotherapy, hyperthermia, or by administration of an adjunctive agent.

3. The method of claim 1, wherein the inhibitor of TFPI is an antibody.

4. The method of claim 1, wherein the inhibitor of TFPI is a peptide.

5. The method of claim 1, wherein the inhibitor of TFPI is a peptoid.

6. The method of claim 1, wherein the tumorous tissue is selected from the group consisting of breast cancer, prostate cancer, lung cancer, pancreatic cancer, gastric cancer, colon cancer, ovarian cancer, renal cancer, hepatoma, melanoma, lymphoma, and sarcoma.

7. The method of claim 1, wherein the tumorous tissue is selected from the group consisting of adenocarcinomas including pancreatic, gastric, colon, breast, lung, hepatic, renal, prostatic, or unknown site of origin primary adenocarcinomas.

8. The method of claim 1, wherein the pharmaceutical composition is administered subcutaneously, intravenously, intradermally, orally, or peri- or intra-tumorally.

9. The method of claim 1, wherein the induction or augmentation of tissue factor expression or release occurs by administration of a pharmacological agent effective for induction or augmentation of tissue factor expression or release simultaneously with the administration of the inhibitor of tissue factor pathway inhibitor.

10. The method of claim 1, wherein tissue factor expression or release is induced or augmented by administration of an inhibitor selected from the group

consisting of endotoxin, interleukin-1, interleukin-6, and tumor necrosis factor.

11. The method of claim 1, wherein tissue factor expression or release is induced or augmented by administration of a cytokine that is capable of stimulating such expression or release.

12. The method of claim 2, wherein the adjunctive agent is a chemotherapeutic or an immunotherapeutic agent.

13. The method of claim 2, wherein the agent is one selected from the group consisting of endotoxin, interleukin-1, interleukin-6, and tumor necrosis factor.

14. The method of claim 2, wherein the agent is a chemotherapeutic agent selected from the group consisting of DES, 5-fluorouracil, methotrexate, interferon-.alpha., aspariginase, tamoxifen, CMF and flutamide.

15. A pharmaceutical composition comprising a therapeutically effective amount of an inhibitor of tissue factor pathway inhibitor (TFPI), a pharmaceutically acceptable carrier, and an adjunctive agent capable of inducing or augmenting expression or release of tissue factor, or an adjunctive agent capable of inducing tissue necrosis.

16. The pharmaceutical composition of claim 15, wherein the adjunctive agent is a chemotherapeutic or immunotherapeutic agent.

17. The pharmaceutical composition of claim 15, wherein the agent is selected from the group consisting of endotoxin, interleukin-1, interleukin-6, and tumor necrosis factor.

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L18: Entry 28 of 34 File: USPT Nov 6, 2001

US-PAT-NO: 6314315
DOCUMENT-IDENTIFIER: US 6314315 B1

TITLE: Ductal orifice identification by characteristic electrical signal

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hung; David	Belmont	CA		
Stern; Roger A	Cupertino	CA		
Grosser; Morton	Menlo Park	CA		

US-CL-CURRENT: 600/547; 128/898, 600/554

CLAIMS:

What is claimed is:

1. A method of identifying a ductal orifice on a nipple of a mammalian breast said method comprising:

engaging a reference electrode against a surface on the body of the mammal;

engaging a test electrode to a test location on a nipple surface;

applying at least one of an electrical current and a potential between the reference electrode and the test electrode;

measuring a characteristic electrical signal produced in response to the at least one of the applied electrical current and the potential; and

comparing the measured value to a base electrical value in order to determine a likelihood that the test location on the nipple surface comprises a ductal orifice.

2. A method as in claim 1, wherein the base electrical value is a predetermined value.

3. A method as in claim 1, wherein the reference electrode is engaged on the body of the mammal at a location selected from the group consisting of the base of the breast, the base of the nipple, the surface of the nipple, the areola of the nipple, and an abdominal or chest surface of the mammal.

4. A method as in claim 1, wherein engaging the test electrode comprises sequentially engaging the test electrode at different locations on the nipple surface so that an array of measured values is produced in order to determine a likelihood that any given location comprises a ductal orifice.

5. A method as in claim 4, wherein the base electrical value is a predetermined value.

6. A method as in claim 1, wherein the test electrode comprises multiple

electrodes placed at the surface of the nipple.

7. A method as in claim 6, wherein the multiple electrodes conform to the surface of the nipple.

8. A method as in claim 1, wherein measuring a characteristic electrical signal comprises making measurements at a specific frequency or at a range of frequencies.

9. A method as in claim 1, wherein comparing the measured valve to a base electrical value further comprises capturing an image of the measured value.

10. A method as in claim 1, wherein comparing the measured valve to a base electrical value further comprises receiving a numerical value of the comparison.

11. A method as in claim 1, further comprising receiving an audible signal indicator upon likelihood that the location on the nipple surface comprises a ductal orifice.

12. A kit for identifying a ductal orifice on a breast nipple comprising:

a reference electrode capable of being engaged against a body surface;

a test electrode capable of being engaged against different locations on the breast nipple, wherein both electrodes are capable of being connected to a source that creates an electrical potential between the two electrodes; a unit for measuring a characteristic electrical signal; and a marking element capable of marking the duct location on the nipple surface once the orifice is identified.

13. A kit as in claim 12, further comprising an accessing element for accessing the ductal orifice once identified.

14. A kit as in claim 13, wherein the accessing element comprises an element capable of accessing a ductal orifice selected from the group consisting of a guidewire, a cannula, and a catheter.

15. A kit as in claim 12 wherein the marking element comprises an element selected from the group consisting of a pen capable of leaving an ink marking on the nipple surface and a tool capable of generating a tattoo marking on the nipple surface.

16. A kit as in claim 12, wherein the reference electrode and test electrodes comprise a non-conductive wire mesh screen, and wherein the kit further comprises a conductive gel for placing on the nipple surface for generating a map of the nipple surface.

17. A kit as in any of claims 12-14, 15 or 16, further comprising instructions for use.

18. A kit as in claim 12, further comprising instructions for use setting forth a method comprising:

engaging the reference electrode against a surface on a body of a mammal;

engaging the test electrode to a test location on a nipple surface;

applying at least one of an electrical current and a potential between the reference electrode and the test electrode;

measuring a characteristic electrical signal produced in response to the at least one of the applied electrical current and the potential; and

comparing the measured value to a base value in order to determine a likelihood

that the test location on the nipple surface comprises a ductal orifice.

19. A kit for identifying a ductal orifice on a breast nipple comprising:

a reference electrode capable of being engaged against a body surface;

a test electrode capable of being engaged against different locations on the breast nipple, wherein both electrodes are capable of being connected to a source that creates an electrical potential between the two electrodes; a unit for measuring a characteristic electrical signal; and

an accessing element for accessing the ductal orifice once identified.

20. A kit as in claim 19, wherein the accessing element comprises an element capable of accessing a ductal orifice selected from the group consisting of a guidewire, a cannula, and a catheter.

21. A kit as in claim 19, further comprising a marking element capable of marking the duct location on the nipple surface once the orifice is identified.

22. A kit as in claim 21, wherein the marking element comprises an element selected from the group consisting of a pen capable of leaving an ink marking on the nipple surface and a tool capable of generating a tattoo marking on the nipple surface.

23. A kit as in claim 19, wherein the reference electrode and test electrodes comprises a non-conductive wire mesh screen, and wherein the kit further comprises a conductive gel for placing on the nipple surface for generating a map of the nipple surface.

24. A kit as in any of claims 19-23, further comprising instructions for use.

25. A kit as in claim 19, further comprising instructions for use setting forth a method comprising:

engaging the reference electrode against a surface on a body of a mammal;

engaging the test electrode to a test location on a nipple surface;

applying at least one of an electrical current and a potential between the reference electrode and the test electrode;

measuring a characteristic electrical signal produced in response to the at least one of the applied electrical current and the potential; and

comparing the measured value to a base value in order to determine a likelihood that the test location on the nipple surface comprises a ductal orifice.

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L18: Entry 27 of 34 File: USPT Dec 11, 2001

US-PAT-NO: 6328709
DOCUMENT-IDENTIFIER: US 6328709 B1

TITLE: Devices and methods to identify ductal orifices during nipple aspiration

DATE-ISSUED: December 11, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hung; David	Belmont	CA		
Love; Susan M.	Pacific Palisades	CA		
Nikolchev; Julian	Portola Valley	CA		
George; William R.	Santz Cruz	CA		

US-CL-CURRENT: 604/74; 604/514

CLAIMS:

What is claimed is:

1. A device for aspirating and retrieving breast duct fluid comprising:

an enclosure adapted to be seal against the base of a human breast nipple, said enclosure comprising an interior volume, an aperture adapted to circumscribe the human breast nipple, a vacuum port for connection to a vacuum source for creating a vacuum in said interior volume, and a magnifying lens forming a portion of the enclosure, wherein the magnifying lens is positioned to permit a practitioner to observe the nipple within the aperture.

2. A device as in claim 1, wherein the enclosure has at least one access port for providing access to a nipple surface with a tool and the device further comprises a pneumatic seal within the at least one access port to maintain a vacuum before and during access with the tool.

3. A device as in claim 2, wherein the at least one access port is adapted to receive a tool selected from the group consisting of a ductal orifice marking tool and a ductal fluid retrieval tool.

4. A device for aspirating and retrieving breast duct fluid comprising:

an enclosure adapted to be seal against the base of a human breast nipple, said enclosure comprising an interior volume, an aperture adapted to circumscribe the human breast nipple, and a vacuum port for connection to a vacuum source for creating a vacuum in said interior volume;

a window in the enclosure that provides visual access to a nipple surface; and

an anchor structure on the exterior of the device to which a magnifying tool can be removably attached so that a practitioner can see a magnified nipple through a surface of the window under a vacuum.

5. A device as in claim 4, wherein the enclosure has at least one access port for providing access to the nipple surface with a tool and the device further

comprises a pneumatic seal within the at least one access port to maintain a vacuum before and during access with the tool.

6. A device as in claim 5, wherein the at least one access port is adapted to receive a tool selected from the group consisting of a ductal orifice marking tool and a ductal fluid retrieval tool.

7. A device as in claim 1 or 4, further comprising skirt of a flexible material connected to the aperture, wherein the flexible material is capable of maintaining a seal with the breast skin.

8. A device as in claim 1, wherein the magnifying lens is positioned at an angle relative to a plane of the aperture.

9. A device as in claim 1, wherein the device further comprises threads disposed adjacent the vacuum port for screwing a compatibly threaded vacuum source into the port.

10. A device as in any of claims 1-6 and 8-9, further comprising a package holding the device wherein the device is sterilized and maintained in the package.

11. A method of identifying a breast milk duct having a ductal orifice wherein the duct is capable of yielding fluid or releasing a keratin plug upon aspiration in a vacuum, said method comprising:

(a) placing a device for aspirating and retrieving breast duct fluid on a breast of a patient so that a nipple is received within said device, said device comprising an enclosure for sealing against a base of the nipple, said enclosure comprising an aperture adapted to circumscribe the nipple, a vacuum port for connecting to a vacuum source and a magnification tool,

(b) applying a vacuum to the device through the vacuum port, and

(c) viewing a surface of the nipple through said magnification tool while the device remains in place to identify at least one ductal orifice from which fluid is secreted or a keratin plug is released under the vacuum.

12. A method as in claim 11, further comprising performing a task selected from the group consisting of marking, accessing and collecting fluid from the duct by placing a tool through an access port and contacting the nipple surface to perform the task while the device remains in place on the nipple.

13. The method of claim 12, wherein marking comprises marking the ductal orifice with a reagent or tool selected from the group consisting of dye, ink, pen, plug, and wire.

14. The method of claim 12, wherein accessing the duct comprises accessing the duct with a tool selected from the group consisting of a tool comprising a lumen, a tool comprising a shaft without a lumen, and a fiberoptic endoscope.

15. The method of claim 12, wherein collecting fluid from the duct comprises collecting fluid with a tool comprising a lumen or an absorbent material.

16. The method of claim 11, wherein the device was sterilized prior to placing the device on the nipple.

17. A method of identifying a breast milk duct having a ductal orifice wherein the duct is capable of yielding fluid or releasing a keratin plug upon aspiration in a vacuum, said method comprising:

(a) placing a device for aspirating and retrieving breast duct fluid on a breast of a patient so that a nipple is received in said device, said device comprising an enclosure for sealing against a base of the nipple, said enclosure comprising an aperture adapted to circumscribe the nipple, a vacuum port for connecting to

a vacuum source, and at least one access port for providing access to a surface of the nipple with a tool, the at least one access port including a pneumatic seal for maintaining a vacuum before and during access with the tool;

(b) applying a vacuum to the device through the vacuum port, and

(c) viewing the nipple through a magnification tool while the device remains in place to identify at least one ductal orifice from which fluid is secreted or a keratin plug is released under the vacuum.

18. A device as in claim 4, wherein the magnifying tool comprises a loupe, a lens or a microscope.

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L18: Entry 26 of 34 File: USPT May 21, 2002

US-PAT-NO: 6391026
DOCUMENT-IDENTIFIER: US 6391026 B1

TITLE: Methods and systems for treating breast tissue

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hung; David	Belmont	CA		
Ken; Chris	San Mateo	CA		
Nikolchev; Julian	Portola Valley	CA		
Love; Susan	Pacific Palisades	CA		
O'Leary; Shawn	San Jose	CA		

US-CL-CURRENT: 606/41; 606/13, 606/14, 606/2, 606/20, 606/27, 606/32

CLAIMS:

What is claimed is:

1. A method for treating a breast duct, said method comprising:

selecting an individual duct;

positioning a device within said duct; and

transferring energy to or from cells lining the duct in an amount sufficient to ablate or inhibit proliferation of said cells.

2. A method as in claim 1, wherein transferring energy comprises transferring energy substantially throughout an entire ductal network.

3. A method as in claim 1, wherein transferring energy comprises transferring energy within only a portion of the entire ductal network.

4. A method as in claim 3, further comprising identifying the portion of the ductal network to be treated, wherein energy is transferred only to that portion.

5. A method as in claim 1, wherein transferring energy comprises introducing energy to a lumen of the duct.

6. A method as in claim 5, wherein introducing energy comprises filling at least a portion of a ductal network with an electrically conductive medium and applying high frequency current to the medium.

7. A method as in claim 6, wherein from 50 W to 300 W of energy is applied.

8. A method as in claim 6, wherein applying the high frequency current comprises contacting the electrically conductive medium with an electrode that forms a portion of the device, and said method further comprises the steps of introducing the electrode through a ductal orifice and applying electrical

current between the electrode and a dispersive electrode on the patient's skin or within a breast.

9. A method as in claim 8, wherein the dispersive electrode is disposed on the exterior of the breast.

10. A method as in claim 9, wherein the dispersive electrode is disposed circumferentially about the breast.

11. A method as in claim 1, wherein transferring energy comprises introducing a radiation source into the ductal lumen.

12. A method as in claim 11, wherein the radiation source comprises a radioisotope.

13. A method as in claim 11, wherein the radiation source comprises an X-ray source.

14. A method as in claim 1, wherein transferring energy comprises removing heat from at least a portion of an epithelial lining of an entire ductal network.

15. A method as in claim 14, wherein removing heat comprises introducing a cold fluid through the ductal network.

16. A method as in claim 14, wherein removing heat comprises introducing a fluid through the ductal network and thereafter freezing the fluid.

17. A method as un claim 1 wherein said device comprises an electrically conductive probe.

18. A method as in claim 17 wherein said electrically conductive probe comprises a lumen electrode.

19. An improved method for treating breast tissue comprising a step of applying energy to the breast tissue, wherein the improvement comprises:

introducing a conductive medium into a breast duct; and

wherein said applying step includes applying the energy through said conductive medium located within said breast duct.

20. An improved method as in claim 19, wherein the energy is applied throughout substantially an entire ductal network.

21. An improved method as in claim 19, wherein the energy is high frequency electrical energy.

22. An improved method as in claim 19, wherein said conductive medium is an electrically conductive medium, and wherein said step of applying energy includes a step of applying electrical energy through said electrically conductive medium.

23. An improved method as in claim 22, wherein applying the electrical energy comprises contacting the electrically conductive medium with an electrode introduced through a ductal orifice.

24. An improved method as in claim 23, further comprising disposing a dispersive electrode on an exterior surface of the breast, wherein a current passes between the electrically conductive medium and the dispersive electrode.

25. An improved method as in claim 24, wherein the energy has a power in the range from 50 W to 300 W.

26. A method for treating a breast duct of a patient, said method comprising:

introducing into a breast duct targeted for treatment an agent sensitive to at least one selected from the group consisting of light energy, electrical energy, electromagnetic energy, radiation energy and vibrational energy; and

transferring the specific light, electrical, electromagnetic, radiation or vibrational energy to the agent in the duct in an amount sufficient to disrupt the agent whereupon the agent acts on target cells lining the breast duct.

27. A method as in claim 26, wherein the agent acts ablatively on the target cells lining the breast duct.

28. A method as in claim 26, wherein the agent acts to inhibit proliferation of the target cells lining the breast duct.

29. A method as in claim 26, wherein the agent acts prophylactically on the target cells lining the breast duct.

30. A method as in claim 26, wherein the agent contacts substantially all of the ductal network.

31. A method as in claim 26, wherein the agent contacts a portion of the entire ductal network.

32. A method as in claim 26, further comprising identifying the portion of the ductal network to be treated, wherein energy is transferred only to that portion.

33. A method as in claim 26, wherein transferring energy comprises introducing energy to a lumen of the duct.

34. A method as in claim 26, wherein transferring energy comprises exposing the breast to an energy source.

35. A method as in claim 26, wherein the agent is sensitive to vibrational energy and comprises collagen spheres.

36. A method as in claim 26, wherein the agent is sensitive to light energy comprising wavelengths in the range from ultraviolet to infrared.

37. A method as in claim 35, wherein the agent comprises a photoactive agent selected from the group consisting of porfimer sodium (PHOTOFRIN.RTM.), lutetium texaphrin (lutex or Antrin.RTM.), temoporfin (Foscan.RTM.), and aminolevulinic acid HCl (Levulan.RTM.).

38. A method as in claim 26, wherein the agent introduced in the breast duct comprises a resonant frequency of an electromagnetic energy, and electromagnetic energy is transferred to the breast duct.

39. A method as in claim 37, wherein the electromagnetic energy comprises radiofrequency waves or microwaves.

40. A method as in claim 37, wherein the agent comprises a metallic fluid.

41. A method as in claim 39, wherein the metal is gold or silver.

42. A method as in claim 26, wherein the agent is a radiation sensitizer, and the energy comprises x-ray radiation or gamma radiation.

43. A method as in claim 41, wherein the radiation sensitizer comprises gadolinium.

44. A method as in claim 41, wherein the radiation sensitizer comprises texaphyrin.

45. A method for treating a breast duct, said method comprising:

selecting an individual duct; and

transferring energy to or from cells lining the duct in an amount sufficient to ablate or inhibit proliferation of said cells, wherein said energy is transferred to or from a device positioned within said duct.

46. A method as in claim 45 further comprising a step of introducing a medium into said duct.

47. A method as in claim 46 wherein the medium is an electrically conductive fluid.

48. A method as in claim 46 further comprising a step of positioning at least a portion of said device in said medium and applying a high frequency current to said medium.

49. A method as in claim 48 wherein said device is an electrically conductive probe.

50. A method for treating a breast duct, said method comprising:

selecting a breast duct;

introducing a medium into said breast duct; and

transferring energy to or from cells lining the duct in an amount sufficient to ablate or inhibit proliferation of said cells.

51. A method as in claim 50 wherein said medium is electrically conductive.

52. A method as is claim 51 wherein said medium is a fluid introduced into the duct through a ductal opening.

53. A method as in claim 51 further comprising a step of introducing a therapeutic device into said duct through a ductal opening and contacting said medium with at least a portion of said therapeutic device.

54. A method as in claim 53 wherein said transferring step includes the step of transferring a high frequency electrical current from said therapeutic device to said medium.

55. A method of treating a breast duct, said method comprising:

selecting a breast duct;

introducing a medium into said breast duct;

introducing a device into said breast duct so that at least a portion of said device contacts said medium; and

transferring energy to or from cells lining the duct in an amount sufficient to ablate or inhibit proliferation of said cells.

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L18: Entry 25 of 34 File: USPT Jun 4, 2002

US-PAT-NO: 6398765
DOCUMENT-IDENTIFIER: US 6398765 B1

TITLE: Apparatus, methods and kits for simultaneous delivery of a substance to multiple breast milk ducts

DATE-ISSUED: June 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hung; David	Belmont	CA		

US-CL-CURRENT: 604/284; 604/74

CLAIMS:

What is claimed is:

1. An apparatus for simultaneously accessing two or more ductal networks in a breast, said apparatus comprising:

a manifold having an inlet for receiving fluid and at least two outlets;

at least two individual access probes, each probe having a lumen connected to a respective one of said at least two outlets and configured for insertion through an orifice of a ductal network; and

a collection tube connected to at least one probe for receiving biological material from within the breast.

2. An apparatus as in claim 1, wherein the manifold has at least three outlets connectable to at least three respective probes.

3. An apparatus as in claim 1, wherein the manifold has at least twelve outlets connectable to at least 12 respective probes.

4. An apparatus as in claim 1, wherein the probes are removably connectable to the manifold.

5. An apparatus as in claim 1, wherein at least one probe comprises a fluid control device capable of controlling fluid flow in the lumen of said at least one probe.

6. An apparatus as in claim 1, wherein a number of the probes are each connected to a respective one of the outlets, and said number is equal to the number of the ductal networks to be accessed.

7. An apparatus as in claim 6, wherein at least one of said outlets is unconnected to a respective one of said probes, and the at least one unconnected outlet is closed to fluid flow.

8. An apparatus as in claim 6 wherein the collection tube further comprises a fluid control device capable of controlling fluid flow in the collection tube.

9. An apparatus as in claim 7 wherein at least one of said probes further comprises a fluid control device capable of controlling fluid flow in said lumen of said at least one probe.

10. An apparatus as in claim 6 further comprising a plurality of collection tubes, wherein each collection tube is connected to a respective one of said probes.

11. An apparatus as in claim 10 wherein each probe comprises a fluid control device capable of controlling fluid flow in the lumen of said probe, and each collection tube comprises a fluid control device capable of controlling fluid flow in said collection tube.

12. An apparatus as in claim 10 wherein at least one of said outlets is unconnected to a respective one of said probes and the at least one unconnected outlet is closed to fluid flow.

13. An apparatus as in claim 3, wherein the probes are removably connectable to the manifold and wherein at least one of said outlets is configured, upon removal of a probe therefrom, for closure to fluid flow.

14. An apparatus as in claim 1 wherein the collection tube further comprises a fluid control device capable of controlling fluid flow in said collection tube, and wherein at least one of said probes further comprises a fluid control device capable of controlling fluid flow in the lumen of said at least one of said probes.

15. An apparatus as in claim 1 further comprising at least two collection tubes, each connected to a respective one of the at least two probes, for receiving biological material from within the breast.

16. An apparatus as in claim 1 wherein each probe comprises a fluid control device capable of controlling fluid flow in the respective lumen of the probe.

17. An apparatus as in claim 1 wherein each probe comprises a fluid control device capable of controlling fluid flow in the lumen of said probe, and the collection tube comprises a fluid control device capable of controlling fluid flow in said collection tube.

18. An apparatus as in claim 18, further comprising a first device connectable to the manifold for infusing fluid within the breast.

19. An apparatus as in claim 18, wherein the manifold has at least three outlets connectable to at least three respective probes.

20. An apparatus as in claim 18, wherein the manifold has at least 12 outlets connectable to at least 12 respective probes.

21. An apparatus as in claim 18 wherein the collection tube further comprises a fluid control device capable of controlling fluid flow in the collection tube.

22. An apparatus as in claim 18, wherein the number of outlets exceeds the number of probes and at least one of the outlets is unconnected to a probe and closed to fluid flow.

23. An apparatus as in claim 18 wherein said first device is capable of containing a wash agent.

24. An apparatus as in claim 18 wherein said first device is capable of containing a diagnostic agent.

25. An apparatus as in claim 18 wherein said first device capable of containing an agent for occupying space in a duct.

26. An apparatus as in claim 18, wherein the first device is a syringe.

27. An apparatus as in claim 18, further comprising a second device connectable to the collection tube for collecting biological material from within the breast.

28. An apparatus as in claim 27 further comprising a plurality of collection tubes, each connected to a respective one of said probes, and wherein each collection tube comprises a second device connectable to said collection tube for collecting biological material from within the breast.

29. An apparatus as in claim 27, wherein the second device is a syringe.

30. An apparatus as in claim 1, wherein said manifold is capable of containing a wash agent.

31. An apparatus as in claim 1, wherein said manifold is capable of containing a diagnostic agent.

32. An apparatus as in claim 1, wherein said manifold is capable of containing an agent for occupying space in a duct.

33. A kit for performing ductal lavage or other medical procedures comprising:

a manifold having an inlet and at least twelve outlets; and

at least twelve access probes, each of said probes having a lumen and being connectable to one of said manifold outlets, and each probe being configured for insertion through an orifice of a ductal network of a breast.

34. A kit as in claim 33, further comprising a separate collection receptacle for each probe.

35. A kit as in claim 33, wherein each outlet can be configured, when not connected to a probe, to prevent fluid flow.

36. A kit as in claim 33, wherein at least one of said probes comprises a fluid control device capable of controlling fluid flow through the lumen of said at least one of said probes.

37. A kit as in claim 33, wherein each probe further comprises a collection tube connected thereto, and at least one collection tube further comprises a fluid control device capable of controlling fluid flow in said at least one collection tube.

38. A kit as in claim 33, further comprising a plurality of collection tubes, each connected to a respective one of said probes, wherein at least one collection tube further comprises a fluid control device capable of controlling fluid flow in said collection tube, and at least one probe further comprises a fluid control device capable of controlling fluid flow in the lumen of said at least one probe.

39. A kit as in claim 33, further comprising a supply of a wash agent.

40. A kit as in claim 33, further comprising a supply of a dekeratinizing agent.

41. A kit as in claim 33, further comprising a supply of a diagnostic agent.

42. A kit as in claim 33, further comprising a supply of an agent for occupying space in a duct.

43. An apparatus for simultaneously accessing two or more ductal networks in a breast for ductal lavage or other medical procedures, said apparatus comprising:

a manifold having an inlet for receiving fluid and at least two outlets;

at least two individual probes configured for insertion through an orifice of a ductal network, each probe having at least first and second lumens; and

a collection tube connected to the second lumen of at least one probe.

44. An apparatus as in claim 43, wherein the manifold has at least three outlets connectable to at least the first lumen of at least three probes.

45. An apparatus as in claim 43, wherein the manifold has at least twelve outlets connectable to at least the first lumen of at least 12 probes.

46. An apparatus as in claim 43, wherein the probes are removably connectable to the manifold.

47. An apparatus as in claim 43, wherein at least one of the probes has a fluid control device which controls fluid flow in at least the first lumen of said at least one probe.

48. An apparatus capable of simultaneously accessing two or more ductal networks in a breast as part of a ductal lavage or other medical procedure, said apparatus comprising:

at least two access probes, each access probe having a lumen and being configured for insertion through an orifice of a ductal network;

a manifold having an inlet for receiving fluid and at least two outlets, each of said outlets connected to one of the probes;

a device connectable to the manifold for infusing fluid within the breast; and

a device in communication with the lumen of one of said probes for collecting biological material from within the breast.

49. An apparatus as in claim 48, wherein the infusing device comprises a syringe.

50. An apparatus as in claim 48, wherein the manifold has at least three outlets connectable to at least three respective probes.

51. An apparatus as in claim 48, wherein the manifold has at least twelve outlets connectable to at least 12 respective probes.

52. An apparatus as in claim 51, wherein the probes are removably connectable to the manifold and wherein at least one of said outlets is configured, upon removal of a probe therefrom, for closure to fluid flow.

53. An apparatus as in claim 48, wherein the manifold has at least 3 outlets connectable to at least 3 probes, the number of outlets is greater than the number of probes, and at least one outlet is unconnected to a probe and closed to fluid flow.

54. An apparatus as in claim 48, wherein the probes are removably connectable to the manifold.

55. An apparatus as in claim 48, wherein at least one of said probes comprises a fluid control device capable of controlling fluid flow therein.

56. An apparatus as in claim 48, wherein a number of the probes are each connected to a respective one of the outlets, and said number is equal to the number of the ductal networks to be accessed.

57. An apparatus as in claim 56 wherein at least one of said probes further comprises a fluid control device capable of controlling fluid flow therein.

58. An apparatus as in claim 48 wherein each probe comprises a fluid control

device capable of controlling fluid flow in the lumen of the respective probe.

59. An apparatus as in claim 48, wherein said infusing device is capable of containing a wash agent.

60. An apparatus as in claim 48, wherein said infusing device is capable of containing a diagnostic agent.

61. An apparatus as in claim 48, wherein said infusing device is capable of containing an agent for occupying space in a duct.

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L18: Entry 24 of 34 File: USPT Jul 2, 2002

US-PAT-NO: 6413228
DOCUMENT-IDENTIFIER: US 6413228 B1

TITLE: Devices, methods and systems for collecting material from a breast duct

DATE-ISSUED: July 2, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: 600/562; 435/7.23, 600/573, 604/28

CLAIMS:

What is claimed is:

1. A ductal access device for accessing a breast duct and collecting biological material from within the duct said device comprising:

an elongated member comprising an outer diameter sized for positioning within the breast duct and an internal lumen for infusing fluid into the breast duct and retrieving the biological material from within the breast duct; and

a body for infusing fluid into said elongated member, said body comprising four openings in communication with said internal lumen of said elongated member.

2. The ductal access device of claim 1 wherein one of said openings includes a fluid tight seal.

3. The ductal access device of claim 2 wherein said fluid tight seal includes an opening for receiving a stiffening member.

4. The ductal access device of claim 3 wherein said stiffening member includes a tapered dilator.

5. The ductal access device of claim 1 wherein one of said openings includes a fluid infusion port and another of said openings includes a fluid collection port.

6. The ductal access device of claim 5 further comprising a compressible lumen extending from said fluid infusion port for connecting said fluid infusion port to a fluid containing device, wherein said compressible lumen can be used to control fluid flow to the infusion port.

7. The ductal access device of claim 5 further comprising a compressible lumen

extending from said fluid collection port for connecting said fluid collection port to a fluid collection device, wherein said compressible lumen can be used to control fluid flow from said fluid collection port.

8. The ductal access device of claim 5 wherein said infusion and collection ports each include a longitudinal axis that extends into said body at an angle to a longitudinal axis of said body.

9. The ductal access device of claim 5 wherein said infusion port and said collection port are spaced from each other along a length of said body.

10. The ductal access device of claim 5 wherein said infusion port is proximate said elongated member relative to said collection port.

11. The ductal access device of claim 1 wherein one of said openings includes a port positioned at a distal end of said body and proximate an end of said elongated member.

12. The ductal access device of claim 1 wherein said elongated member includes only one lumen.

13. The ductal access device of claim 1 further comprising an anchor attached to one of said body or said elongated member for securing the ductal access device relative to a patient.

14. The ductal access device of claim 1 wherein said body includes an outer diameter that is greater than an outer diameter of said elongated member.

15. The ductal access device of claim 1 wherein said elongated member includes an atraumatic distal tip.

16. The ductal access device of claim 1 wherein said body has a volume of from about 0.01 ml. to about 1.0 ml.

17. A device for accessing a breast duct and performing ductal lavage, said device comprising:

a fluid hub comprising a proximal end, a distal end and at least three openings; and

an elongated member for positioning within the breast duct comprising an internal lumen for infusing fluid into the breast duct and retrieving fluid from within the duct, said lumen being in communication with said openings of said fluid hub, and a length sized such that a distal end of said elongated member is positioned distal a ductal sphincter and proximal a portion of the breast duct to be lavaged when said distal end of said hub is proximate a ductal opening on a nipple surface.

18. The device of claim 17 wherein said at least three openings include a fluid infusion port and a fluid collection port.

19. The device of claim 18 further comprising a compressible lumen extending from said fluid infusion port for connecting said fluid infusion port to a fluid containing device, wherein said compressible lumen can be used to control fluid flow to the infusion port.

20. The device of claim 18 further comprising a compressible lumen extending from said fluid collection port for connecting said fluid collection port to a fluid collection device, wherein said compressible lumen can be used to control fluid flow from said fluid collection port.

21. The device of claim 18 wherein said infusion port and said collection port are spaced from each other along a length of said hub.

22. The device of claim 21 wherein said infusion port is positioned proximate

said elongated member relative to said collection port.

23. The device of claim 17 wherein said elongated member includes only one lumen.

24. The device of claim 17 further comprising an anchor attached to one of said hub or said elongated member for securing said device relative to a patient.

25. The device of claim 17 wherein said hub includes an outer diameter that is greater than an outer diameter of said elongated member.

26. The device of claim 17 wherein said elongated member includes an atraumatic distal tip.

27. The device of claim 17 wherein said hub has an inner volume of from about 0.01 ml. to about 1.0 ml.

28. The device of claim 17 wherein said at least three openings include four openings.

29. The device of claim 28 wherein one of said openings includes a fluid tight seal.

30. The device of claim 29 wherein said fluid tight seal includes an opening for receiving a stiffening member.

31. The device of claim 30 wherein said stiffening member includes a tapered dilator.

32. A device for accessing a breast duct having multiple branches and performing ductal lavage within said duct, said device comprising:

an elongated member comprising an outer diameter sized for positioning within the breast duct and having an internal lumen for infusing a fluid into the breast duct and retrieving cellular material from within the branches; and

a body for infusing fluid into said elongated member, said body comprising at least three openings for communicating with said internal lumen and dimensions such that said elongated member remains within the breast duct and capable of retrieving the cellular material from within the branches of the duct being lavaged after said elongated member has been positioned within said duct and said body is free of external support from a practitioner or assistant.

33. The device of claim 32 wherein one of said openings is at a distal end of said body proximate said elongated member.

34. The device of claim 32 wherein one of said openings includes a fluid infusion port and another of said openings includes a fluid collection port.

35. The device of claim 34 further comprising a compressible lumen extending from said fluid infusion port for connecting said fluid infusion port to a fluid containing device, wherein said compressible lumen can be used to control fluid flow to the infusion port.

36. The device of claim 34 further comprising a compressible lumen extending from said fluid collection port for connecting said fluid collection port to a fluid collection device, wherein said compressible lumen can be used to control fluid flow from said fluid collection port.

37. The device of claim 34 wherein said infusion and collection ports each include a longitudinal axis that extends into said body at an angle to a longitudinal axis of said body.

38. The device of claim 34 said infusion port and said collection port are spaced from each other along a length of said body.

39. The device of claim 34 wherein said infusion port is proximate said elongated member relative to said collection port.

40. The device of claim 34 wherein said elongated member includes only one lumen.

41. The device of claim 32 wherein said elongated member includes only one lumen.

42. The device of claim 32 further comprising an anchor attached to one of said body or said elongated member for securing the device relative to a patient.

43. The device of claim 32 wherein said body includes an outer diameter that is greater than an outer diameter of said elongated member.

44. The device of claim 32 wherein said elongated member includes an atraumatic distal tip.

45. The device of claim 32 wherein said body has an inner volume of from about 0.01 ml. to about 1.0 ml.

46. The device of claim 32 wherein said at least three openings includes four openings.

47. The device of claim 32 wherein one of said openings includes a fluid-tight seal.

48. The device of claim 47 wherein said fluid tight seal includes an opening for receiving a stiffening member.

49. The device of claim 48 wherein said stiffening member includes a tapered dilator.

50. A ductal access device for accessing a breast duct and collecting biological material from within the duct, said device comprising:

an elongated member comprising an outer diameter sized for positioning within the breast duct and having an internal lumen for retrieving the biological material from within the duct;

a body for infusing fluid into said elongated member, said body comprising at least three openings in communication with said internal lumen of said elongated member; and

an anchor operatively connected to said elongated member and said body for stabilizing the position of the elongated member within the duct and the body relative to a breast in which the elongated member extends.

51. The ductal access device of claim 50 wherein said anchor includes a securing member configured for being attached to a portion of a body of a patient.

52. The ductal access device of claim 51 wherein the securing member includes a tether having an adhesive for contacting and adhering to the portion of the body of the patient.

53. The ductal access device of claim 50 wherein said anchor extends from one of said body and said elongated member.

54. The ductal access device of claim 50 wherein one of said openings includes a fluid tight seal.

55. The ductal access device of claim 54 wherein said fluid tight seal includes an opening for receiving a dilator.

56. The ductal access device of claim 50 wherein one of said openings includes a fluid infusion port and another of said openings includes a fluid collection port.

57. The ductal access device of claim 56 wherein said infusion port and said collection port are spaced from each other along a length of said body.

58. The ductal access device of claim 57 wherein said infusion port is positioned proximate said elongated member relative to said collection port.

59. The ductal access device of claim 50 wherein said elongated member includes only one lumen.

60. The ductal access device of claim 50 wherein said body includes an outer diameter that is greater than an outer diameter of said elongated member.

61. The ductal access device of claim 50 wherein said elongated member includes an atraumatic distal tip.

62. The ductal access device of claim 50 wherein said body has a volume of from about 0.01 ml. to about 1.0 ml.

63. A ductal access device for accessing a breast duct and collecting cellular material from within the duct, said device comprising:

a single elongated member comprising an outer diameter sized for positioning within the breast duct and an inner diameter for introducing fluid into the duct and receiving cellular material from within the duct; and

a manifold hub for receiving cellular material from the breast duct carried by the elongated member, said manifold hub comprising at least three openings in communication with said elongated member and an inner diameter that is greater than the inner diameter of said elongated member.

64. The ductal access device of claim 63 wherein said inner diameter of said elongated member is from about 0.007 inch to about 0.047 inch.

65. The ductal access device of claim 63 wherein an outer diameter of said hub is greater than the outer diameter of said elongated member.

66. The ductal access device of claim 65 wherein the outer diameter of said elongated member is from about 0.010 inch to about 0.50 inch.

67. The ductal access device of claim 63 wherein said hub has an inner volume of from about 0.01 ml. to about 1.0 ml.

68. The ductal access device of claim 63 wherein said at least three openings include a fluid infusion port and a fluid collection port.

69. The ductal access device of claim 68 further comprising a compressible lumen extending from said fluid infusion port for connecting said fluid infusion port to a fluid containing device, wherein said compressible lumen can be used to control fluid flow to the infusion port.

70. The ductal access device of claim 68 further comprising a compressible lumen extending from said fluid collection port for connecting said fluid collection port to a fluid collection device, wherein said compressible lumen can be used to control fluid flow from said fluid collection port.

71. The ductal access device of claim 68 wherein said infusion port is positioned proximate said elongated member relative to said collection port.

72. The ductal access device of claim 63 further comprising an anchor attached to one of said hub or said elongated member for securing said device relative to a patient.

73. The ductal access device of claim 63 wherein said at least three openings include four openings.

74. The ductal access device of claim 73 wherein one of said four openings includes a fluid tight seal.

75. The ductal access device of claim 74 wherein said fluid tight seal includes an opening for receiving a stiffening member.

76. The ductal access device of claim 75 wherein said stiffening member includes a tapered dilator.

77. The ductal access device of claim 63 wherein said elongated member includes only one lumen.

78. The ductal access device of claim 63 wherein said elongated member includes an atraumatic distal tip.

79. A ductal access device for accessing a breast duct and collecting cellular material from within the duct, said device comprising:

an elongated member comprising an outer diameter sized for positioning within the breast duct and an internal lumen;

a manifold hub comprising a plurality of openings in communication with said internal lumen; and

a stiffening member extending within said internal lumen and past a distal end of said elongated member as said ductal access device is introduced into the breast duct.

80. The ductal access device of claim 79 wherein said stiffening member includes a dilator.

81. The ductal access device of claim 80 wherein said dilator is a tapered dilator.

82. The ductal access device of claim 80 wherein said dilator has an outer diameter at a point along its length of about 0.024 inches or less.

83. The ductal access device of claim 79 wherein said stiffening member has a first diameter at a distal end thereof and a second, larger diameter at a point proximate a distal end of said elongated member.

84. The ductal access device of claim 83 wherein said distal end of said elongated member includes an atraumatic tip.

85. The ductal access device of claim 79 further comprising an anchor for securing said elongated member and said hub relative to a portion of a body of a patient.

86. The ductal access device of claim 79 wherein said plurality of openings includes at least three openings.

87. The ductal access device of claim 86 wherein a first one of said openings includes a fluid infusion port, a second one of said openings includes a fluid collection port and a third one of said openings includes an access port positioned at a distal end of said hub proximate said elongated member.

88. The ductal access device of claim 86 further including a fourth opening at a proximal end of said hub.

89. The ductal access device of claim 88 wherein said fourth opening includes a fluid-tight seal for receiving said stiffening member.

90. The ductal access device of claim 79 wherein said elongated member includes only one lumen.

91. The ductal access device of claim 79 wherein said hub has a volume of from about 0.01 ml. to about 1.0 ml.

92. The ductal access device of claim 79 wherein said hub includes an outer diameter that is greater than an outer diameter of said elongated member.

93. A ductal access device comprising:

a hub comprising an internal elongate manifold and at least three openings; and

an elongated member comprising a distal end including an atraumatic tip, a proximal end, a single lumen in communication with said hub openings and extending between said distal and proximal ends, and dimensions which permit introduction of the distal end through a ductal orifice and positioning a distal end of said elongated member distal to a ductal sphincter and proximal a first bifurcation in a human breast duct.

94. The ductal access device of claim 93 further comprising a dilator for extending from said atraumatic tip as said elongated member is introduced into a breast duct.

95. The ductal access device of claim 94 wherein said dilator has a first diameter at a distal end thereof and a second, larger diameter at a point proximate said atraumatic tip of said elongated member.

96. The ductal access device of claim 93 further comprising an anchor for securing said elongated member and said hub relative to a portion of a body of a patient.

97. The ductal access device of claim 93 wherein said at least three openings includes a fluid infusion port, a fluid collection port and an access port positioned at a distal end of said hub proximate said elongated member.

98. The ductal access device of claim 97 wherein said at least three openings further include a fourth opening.

99. The ductal access device of claim 98 wherein said fourth opening includes a fluid-tight seal at a proximal end of said hub.

100. The ductal access device of claim 93 wherein said hub includes an outer diameter that is greater than an outer diameter of said elongated member.

101. The ductal access device of claim 93 wherein said hub has a volume of from about 0.01 ml. to about 1.0 ml.

L18: Entry 23 of 34 File: USPT Dec 17, 2002

US-PAT-NO: 6494859
DOCUMENT-IDENTIFIER: US 6494859 B2

TITLE: Methods using pressure to obtain fluids and cellular material from breast ducts

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: 604/28; 604/19, 604/27, 604/48, 604/73, 604/74, 604/75, 604/76

CLAIMS:

What is claimed is:

1. A method for obtaining fluid and cellular material from a breast duct including fluid and cellular material from distal areas of the ductal architecture of a breast milk duct comprising: (a) locating at least one milk duct on a nipple of a breast, wherein the milk duct exhibits no observable spontaneous discharge; (b) introducing washing fluid into the milk duct, and providing continuous or intermittent infusion of the wash fluid for a period of time; (c) applying external positive pressure to the breast and repeating application of external pressure periodically, continuously, or cyclically during infusion of the wash fluid; and (d) collecting the washing fluid intraductally from the duct during the infusion and application of external pressure, wherein the washing fluid collected comprises fluid and cells from the duct.

2. The method of claim 1, wherein the pressure is applied manually or mechanically.

3. A method as in claim 1, wherein introducing and collecting comprise access of a breast duct by an access tool having at least one lumen.

4. The method of claim 3, wherein collecting comprises applying suction to an outflow lumen of a dual lumen catheter to draw fluid out from the duct.

5. A method of obtaining material from a milk duct in a breast of a patient comprising: (a) locating at least one ductal orifice on a nipple of the breast, wherein the at least one ductal orifice exhibits no observable spontaneous discharge; (b) introducing an access tool having at least one lumen through one of the ductal orifices and into the ductal passage; (c) introducing a washing fluid through a lumen into the ductal passage; (d) applying external positive pressure to the breast and repeating application of external pressure periodically, continuously, or cyclically during infusion of the wash fluid; and (e) collecting the washing fluid intraductally from the ductal passage through a lumen of the access tool during or after fluid introduction and application of external pressure to the breast.

6. The method according to any claims 1 or 5, wherein the washing fluid comprises a mixture of air fluid.

7. A method as in claim 1, wherein about 5 ml to about 20 ml of washing fluid is introduced into the milk duct.

8. A method as in claim 5, wherein about 5 ml to about 20 ml of washing fluid is introduced into the milk duct.

9. A method as in claim 1, wherein the washing fluid is continuously or intermittently infused in volumes of about 0.5 ml to about 1. 0 ml at a time.

10. A method as in claim 5, wherein the washing fluid is continuously or intermittently infused in volumes of about 0.5 ml to about 1.0 ml at a time.

11. A method as in claim 1, wherein introducing washing fluid comprises introducing a sufficient amount of washing fluid to substantially fill the duct.

12. A method as in claim 5, wherein introducing washing fluid comprises introducing a sufficient amount of washing fluid to substantially fill the duct.

13. A method as in claim 1, wherein the pressure is applied beginning at the base of the breast and moving towards the areola and nipple regions of the breast.

14. A method as in claim 5, wherein the pressure is applied beginning at the base of the breast and moving towards the areola and nipple regions of the breast.

15. A method as in claim 5, wherein the pressure is applied manually.

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CLAIMS:

What is claimed is:

1. An ultrasonic diagnostic imaging system comprising: a transducer which receives ultrasonic echo signals containing fundamental and harmonic signal components; a frequency sensitive circuit, coupled to receive echo signals produced by said transducer, which passes harmonic frequency signal components relative to fundamental frequency signal components; an analog to digital converter coupled to receive echo signals processed by said frequency sensitive circuit; and a digital beamformer coupled to receive digital echo signals produced by said analog to digital converter.

2. The ultrasonic diagnostic imaging system of claim 1, wherein said frequency sensitive circuit comprises an attenuating circuit that exhibits a passband which attenuates fundamental signal components relative to harmonic signal components.

3. The ultrasonic diagnostic imaging system of claim 2, wherein said passband exhibits a lower corner frequency which is above a given fundamental signal frequency and below the second harmonic of said given fundamental signal frequency.

4. The ultrasonic diagnostic imaging system of claim 3, wherein said fundamental signal components occupy a fundamental signal passband and said harmonic signal components occupy a harmonic signal passband; and wherein said corner frequency is above the center frequency of said fundamental signal passband and below the center frequency of said harmonic signal passband.

5. The ultrasonic diagnostic imaging system of claim 1, wherein said frequency sensitive circuit comprises a highpass filter.

6. The ultrasonic diagnostic imaging system of claim 5, wherein said highpass filter exhibits a passband having a lower corner frequency which is above a given fundamental signal frequency and below the second harmonic of said given fundamental signal frequency.

7. The ultrasonic diagnostic imaging system of claim 1, wherein said frequency

sensitive circuit comprises a bandpass filter.

8. The ultrasonic diagnostic imaging system of claim 7, wherein said bandpass filter exhibits a passband having a lower corner frequency which is above a given fundamental signal frequency and below the second harmonic of said given fundamental signal frequency, and said passband includes said second harmonic frequency.

9. The ultrasonic diagnostic imaging system of claim 1, wherein the transducer further comprises an array transducer having a plurality of transducer elements which receive ultrasonic echo signals containing fundamental and harmonic signal components; wherein the digital beamformer further comprises a digital beamformer having a plurality of processing channels coupled to receive ultrasonic echo signals from respective ones of said transducer elements; wherein the analog to digital converter further comprises a plurality of analog to digital converters having outputs coupled to respective ones of said digital beamformer processing channels; and wherein the frequency sensitive circuit further comprises a plurality of attenuating circuits coupled between said transducer elements and said analog to digital converters which attenuate fundamental signal components to a greater degree than harmonic signal components.

10. The ultrasonic-diagnostic imaging system of claim 9, wherein said attenuating circuits comprise highpass filters.

11. The ultrasonic diagnostic imaging system of claim 9, wherein said attenuating circuits comprise bandpass filters.

12. The ultrasonic diagnostic imaging system of claim 1, wherein the frequency sensitive circuit further comprises a circuit, coupled to receive echo signals produced by said transducer, which enhances harmonic signal components relative to fundamental frequency signal components.

13. The ultrasonic diagnostic imaging system of claim 12, wherein the frequency sensitivity of said frequency sensitive circuit is programmable.

14. An ultrasonic diagnostic imaging system comprising: a transducer which receives ultrasonic echo signals containing fundamental and harmonic signal components; a frequency sensitive circuit, coupled to receive echo signals produced by said transducer, which passes harmonic frequency signal components relative to fundamental frequency signal components; an analog to digital converter coupled to receive echo signals processed by said frequency sensitive circuit; and digital echo signal processor coupled to receive digital echo signals produced by said analog to digital converter; wherein the frequency sensitive circuit further comprises a circuit, coupled to receive echo signals produced by said transducer, which enhances harmonic signal components relative to fundamental frequency signal components; wherein the digital echo signal processor further comprises a digital beamformer coupled to receive digital echo signals produced by said analog to digital converter; wherein said analog to digital converter is operated at a sampling frequency; and further comprising a second frequency sensitive circuit, coupled between said transducer and said analog to digital converter, which attenuates signals at said sampling frequency.

15. The ultrasonic diagnostic imaging system of claim 14, wherein said first frequency sensitive circuit comprises a filter circuit having a maximum response above a fundamental frequency; and wherein said second frequency sensitive circuit comprises an anti-aliasing filter.

16. An ultrasonic diagnostic imaging system comprising: a transducer which receives ultrasonic echo signals containing fundamental and harmonic signal components; a frequency sensitive circuit, coupled to receive echo signals produced by said transducer, which passes harmonic frequency signal components relative to fundamental frequency signal components; an analog to digital converter coupled to receive echo signals processed by said frequency sensitive

circuit; and a digital echo signal processor coupled to receive digital echo signals produced by said analog to digital converter; wherein the frequency sensitive circuit further comprises a circuit, coupled to receive echo signals produced by said transducer, which enhances harmonic signal components relative to fundamental frequency signal components; wherein the digital echo signal processor further comprises a digital beamformer coupled to receive digital echo signals produced by said analog to digital converter; wherein said frequency sensitive circuit comprises a plurality of selectable circuits of different frequency sensitivity.

17. An ultrasonic diagnostic imaging system comprising: a transducer which receives ultrasonic echo signals containing fundamental and harmonic signal components; a frequency sensitive circuit, coupled to receive echo signals produced by said transducer, which passes harmonic frequency signal components relative to fundamental frequency signal components; an analog to digital converter coupled to receive echo signals processed by said frequency sensitive circuit; and a digital echo signal processor coupled to receive digital echo signals produced by said analog to digital converter; wherein the transducer comprises a transducer which receives ultrasonic echo signals containing fundamental and harmonic signal components at given frequencies; wherein the frequency circuit further comprises a plurality of tuned circuits, coupled to receive said echo signals, which are tuned to pass harmonic signals of different frequencies; wherein the analog to digital converter is coupled to receive echo signals passed by said tuned circuits; further comprising a tuned circuit selector, coupled to said tuned circuits, which selectively enables passage of harmonic signals by one of said tuned circuits to said analog to digital converter; and wherein the digital echo signal processor further comprises a digital beamformer coupled to receive digital echo signals produced by said analog to digital converter.

18. The ultrasonic diagnostic imaging system of claim 17, wherein said tuned circuit selector comprises a multiplexer.

19. The ultrasonic diagnostic imaging system of claim 17, wherein said transducer exhibits a nominal operating frequency; and wherein said tuned circuit selector acts to enable passage of harmonic signals in correspondence with said nominal operating frequency.

20. The ultrasonic diagnostic imaging system of claim 17, wherein said tuned circuit selector acts to enable passage of harmonic signals in correspondence with depth dependent attenuation effects.

21. The ultrasonic diagnostic imaging system of claim 17, wherein said tuned circuit control acts to enable passage of harmonic signals by said variable tuned circuit in correspondence with depth dependent attenuation effects.

22. An ultrasonic diagnostic imaging system comprising: a transducer which receives ultrasonic echo signals containing fundamental and harmonic signal components; a frequency sensitive circuit, coupled to receive echo signals produced by said transducer, which passes harmonic frequency signal components relative to fundamental frequency signal components; an analog to digital converter coupled-to receive echo signals processed by said frequency sensitive circuit; and a digital echo signal processor coupled to receive digital echo signals produced by said analog to digital converter; wherein the transducer further comprises a transducer which receives ultrasonic echo signals containing fundamental and harmonic signal components at given frequencies; wherein the frequency sensitive circuit further comprises a variable tuned circuit, coupled to receive said echo signals, which is variably tuned to pass harmonic signals relative to corresponding fundamental frequencies; wherein the analog to digital converter is coupled to receive echo signals passed by said variable tuned circuit; further comprising a tuned circuit control, coupled to said variable tuned circuit, which selectively tunes said variable tuned circuit to pass harmonic signals of a desired frequency; and wherein the digital echo signal processor further comprises a digital beamformer coupled to receive digital echo signals produced by said analog to digital converter.

23. The ultrasonic diagnostic imaging system of claim 22, wherein said variable tuned circuit comprises one or more variable resistive or reactive components coupled to said tuned circuit control.

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TITLE: Devices, methods and systems for collecting material from a breast duct

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CLAIMS:

What is claimed is:

1. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a wash fluid to the breast milk duct, wherein a volume of at least 2 ml is present within the duct for a preselected time; and collecting at least a portion of the introduced wash fluid from within the duct, wherein said portion carries the cellular material.

2. A method as in claim 1, wherein the preselected time is less than one second.

3. A method as in claim 1, wherein the preselected time is in the range from one second to one hour.

4. A method as in claim 1, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

5. A method as in claim 1, wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

6. A method as in claim 1, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

7. A method as in claim 1, further comprising separating cellular material from the collected fluid.

8. A method as in claim 7, further comprising examining the separated cellular material.

9. A method as in claim 1, wherein the cellular material is a substance selected from the group consisting of whole cells, cellular debris, proteins, nucleic acids, polypeptides, glycoproteins, lipids, fats, glycoproteins, small organic molecules, metabolites, and macromolecules.

10. A method as in claim 1, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

11. A method as in claim 1, wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

12. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a ductal access device having at least one lumen therethrough into a duct; introducing a wash fluid through the access device lumen into the milk duct, wherein a volume of at least 2 ml is present within the duct for a preselected time; and collecting at least a portion of the wash fluid from the duct through the lumen of the access device.

13. A method as in claim 12, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

14. A method as in claim 12, wherein introducing the ductal access device comprises positioning a distal end thereof distal to the ductal sphincter.

15. A method as in claim 12, wherein the access device has only a single lumen which extends into the duct.

16. A method as in claim 12, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

17. A methods as in claim 12, wherein the preselected time is less than one second.

18. A method as in claim 12, wherein the preselected time is in the range from one second to one hour.

19. A method as in claim 12, wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

20. A method as in claim 12, further comprising separating cellular material from the collected fluid.

21. A method as in claim 20, further comprising examining the separated cellular material.

22. A method as in claim 17, wherein the cellular material is a substance selected from the group consisting of whole cells, cellular debris, proteins, nucleic acids, polypeptides, glycoproteins, lipids, fats, glycoproteins, small organic molecules, metabolites, and macromolecules.

23. A method as in claim 12, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

24. A method as in claim 12, wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and

albuinin.

25. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a wash fluid to the breast milk duct, wherein the wash fluid is present within the duct for a preselected time; and collecting at least a portion of the introduced wash fluid from within the duct, wherein said portion carries the cellular material; wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

26. A method as in claim 25, wherein the volume of wash fluid is at least 2 ml.

27. A method as in claim 25, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

28. A method as in claim 25, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

29. A method as in claim 25, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

30. A method as in claim 25, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

31. A method as in claim 25, wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

32. A method as in claim 25, wherein the preselected time is less than one second.

33. A method as in claim 25, wherein the preselected time is in a range from one second to one hour.

34. A method as in claim 25, further comprising separating cellular material from the collected fluid.

35. A method as in claim 34, further comprising examining the separated cellular material.

36. A method as in claim 25, wherein the cellular material is a substance selected from the group consisiting of whole cells, cellular debris, nucleic acids, lipids, protein metabolites, small organic molecules, and macromolecules.

37. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a ductal access device having at least one lumen therethrough into a duct; introducing a wash fluid through the access device lumen into the milk duct, wherein the wash fluid is present within the duct for a preselected time; and collecting at least a portion of the wash fluid from the duct through the lumen of the access device; wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

38. A method as in claim 37, wherein the volume of wash fluid is at least 2 ml.

39. A method as in claim 37, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

40. A method as in claim 37, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

41. A method as in claim 37, wherein the preselected time is less than one second.

42. A method as in claim 37, wherein the preselected time is in a range from one second to one hour.

43. A method as in claim 37, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

44. A method as in claim 37, wherein introducing the ductal access device comprises positioning a distal end thereof distal to the ductal sphincter.

45. A method as in claim 37 wherein the access device has only a single lumen which extends into the duct.

46. A method as in claim 37, further comprising separating cellular material from the collected fluid.

47. A method as in claim 46, further comprising examining the separated cellular material.

48. A method as in claim 37, wherein the cellular material is a substance selected from the group consisiting of whole cells, cellular debris, nucleic acids, lipids, protein metabolites, small organic molecules, and macromolecules.

49. A method as in claim 37, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

50. A method as in claim wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

51. A kit comprising: a ductal access device; and instructions for use setting forth a method according to claim 12.

52. A ductal access device comprising: an access tube having a distal end, at least one lumen therethrough, and dimensions which permit introduction of the distal end through a ductal orifice and positioning a distal end thereof distal to the ductal sphincter of a human breast.

53. A ductal access device as in claim 52, further comprising means on the access tube for positioning the distal end distal to the ductal sphincter.

54. A ductal access device as in claim 53, wherein the positioning means comprises length indicia on the tube which permit a user to determine the depth to which the distal end of the tube has been introduced.

55. A ductal access device as in claim 53, wherein the positioning means comprises a stop element formed or attached to the tube, wherein the stop has dimensions which prevent further insertion of the tube into the duct and wherein the stop is positioned on the tube so that the distal tip will be located distal to the ductal sphincter when the device is fully inserted up to the stop.

56. A ductal access device as in claim 55, wherein the stop element comprises a collar affixed to or formed on an exterior surface of the tube.

57. A ductal access device as in claim 52, further comprising means for anchoring the device to the breast.

58. A ductal access device as in claim 52, further comprising a receiving portion comprising a water tight seal for receiving the dilator.

59. A ductal access device as in claim 55, wherein the stop element comprises a hub attached to a proximal end of the tube, wherein the hub has a width which is greater than the diameter of the tube so that a shoulder is formed at a junction between the tube and the hub.

60. A ductal access device as in claim 53, wherein the positioning means comprises a nob on the access tube having an increase diameter for anchoring the tube distal to the ductal sphincter once the nob has passed the sphincter and rests distal to it.

61. A ductal access device as in claim 52, wherein the access tube has an outer diameter of 0.05 inches or 1.27 mm or less.

62. A ductal access device as in claim 52, wherein the access tube has an outer diameter of 0.010 inches (or 0.254 mm) or greater.

63. A ductal access device as in claim 53, wherein the outer diameter is in the range from 0.010 inches or 0.254 mm to 0.050 inches or 1.27 mm.

64. A ductal access device as in claim 52, wherein the access tube has a lumen diameter 0.007 inches (or 0.178 mm) or greater.

65. A ductal access device as in claim 52, wherein the access tube has a lumen diameter in the range from 0.007inches or 0.178 mm to 0.047 inches or 1.19 mm.

66. A ductal access device as in claim 52, further comprising: an infusion connector providing a fluid flow path into the lumen of the tube; and a collection connector providing a fluid outlet path from the lumen of the tube, said infusion and collection connectors being isolated from each other so that the fluid may be infused through the infusion connector and simultaneously removed through the collection connector.

67. A ductal access device as in claim 52, further comprising a dilator removably received in the access tube and having a distal tip which is positionable through the access tube to extend from the distal end thereof.

68. A ductal access device as in claim 67, wherein the dilator has an outer diameter of 0.024 inches (or 0.61 mm) or less.

69. A ductal access device as in claim 67, wherein the dilator is tapered.

70. A ductal access device as in claim 67, wherein a receiving portion of the device for receiving the dilator comprises a water-tight seal.

71. A ductal access system comprising: a ductal access device as in claim 52; and a container holding a premeasured volume of ductal wash fluid.

72. A ductal access system as in claim 71, wherein the container comprises a syringe for connection to the first side port.

73. A ducal access system as in claim 71, wherein the pre-measured volume is in the range from 2 ml to 100 ml.

74. A ductal access system as in claim 71, wherein the ductal access fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

75. A ductal access system as in claim 71, wherein the ductal access fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

76. A ductal access device comprising: an access tube having a distal end, a single lumen therethrough, and dimensions which permit introduction of the distal end through a ductal orifice and positioning a distal end thereof distal to the ductal sphincter. an infusion connector providing a fluid flow path into the lumen of the access tube; and a collection connector providing a fluid outlet path from the lumen of the access tube, said infusion and collection connectors being isolated from each other so that fluid may be infused through the infusion connector and simultaneously removed through the collection connector.

77. A ductal access device as in claim 76, wherein the tube has an outer diameter of 0.010 inches or 0.254 mm or greater.

78. A ductal access device as in claim 76, wherein the tube has an outer diameter of 0.050 inches or 1.27 mm or less.

79. A ductal access device as in claim 77, wherein the outer diameter is in the range from 0.010 inches or 0.254 mm to 0.050 inches or 1.27 mm.

80. A ductal access device as in claim 76, wherein the access tube has a lumen diameter 0.007 inches or 0.178 mm or greater.

81. A ductal access device as in claim 79, wherein the access tube has a lumen diameter in the range from 0.007 inches or 0.178 mm to 0.047 inches or 1.1.9 mm.

82. A ductal access device as in claim 76, further comprising means on the access tube positioning a distal end thereof distal to the ductal sphincter.

83. A ductal access device as in claim 82, wherein the positioning means comprises length indicia on the tube which permit a user to determine the depth to which the distal end of the tube has been introduced.

84. A ductal access device as in claim 82, wherein the positioning means comprises a stop element formed or attached to the tube, wherein the stop has dimensions which prevent further insertion of the tube into the duct and wherein the stop is positioned on the tube so that a distal end of the distal tip is positioned thereof distal to the ductal sphincter.

85. A ductal access device as in claim 84, wherein the stop element comprises a collar affixed to or formed on an exterior surface of the tube.

86. A ductal access device as in claim 84, wherein the stop element comprises a hub attached to a proximal end of the tube, wherein the hub has a width which is greater than the diameter of the tube so that a shoulder is formed at a junction between the tube and the hub.

87. A ductal access device as in claim 82, wherein the positioning means comprises a nob on the access tube having an increase diameter for anchoring the tube distal to the ductal sphincter once the nob has passed the sphincter and rests distal to it.

88. A ductal access device as in claim 76, further comprising means for anchoring the device to the breast.

89. A ductal access device as in claim 76, further comprising a dilator removably received in the access tube and having a distal tip which is positionable through the access tube to extend from the distal end thereof.

90. A ductal access device as in claim 89, wherein the dilator has an outer diameter of 0.024 inches (or 0.061 mm) or less.

91. A ductal access device as in claim 89, wherein the dilator is tapered.

92. A ductal access device as in claim 89, wherein a receiving portion of the device for receiving the dilator comprises a water-tight seal.

93. A ductal access system comprising: a ductal access device as in claim 76; and a

container holding a premeasured volume of ductal wash fluid.

94. A ductal access system as in claim 93, wherein the ductal wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

95. A ductal access system as in claim 93, wherein the container comprises a syringe for connection to the first side port.

96. A ductal access system as in claim 93, wherein the premeasured volume is in the range from 2 ml to 100 ml.

97. A ductal access system as in claim 93, wherein the ductal access fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

98. A ductal access device comprising: a hub having an internal elongate manifold, a lower port at a bottom of the manifold, and first and second side ports spaced above the lower port; and an access tube having a distal end, a proximal end, a lumen therethrough, and dimensions which permit introduction of the distal end through a ductal orifice and a positioning a distal end thereof distal to the ductal sphincter of the human breast, wherein the proximal end of the tube is attached to the lower port of the hub.

99. A ductal access device as in claim 98, wherein the first and second side ports are at the same level relative to the lower port.

100. A ductal access device as in claim 98, wherein the first side port is below the second side port.

101. A ductal access device as in claim 98, wherein the access tube has an outer diameter of 0.010 inches or 0.245 mm or greater.

102. A ductal access device as in claim 98, wherein the access tube has an outer diameter of 0.50 inches or 1.27 mm or less.

103. A ductal access device as in claim 101, wherein the outer diameter is in the range from 0.010 inches or 0.245 mm to 0.050 inches or 1.27 mm.

104. A ductal access device as in claim 103, wherein the access tube has a lumen diameter 0.007 inches (0.178 mm) or greater.

105. A ductal access device as in claim 103, wherein the access tube has a lumen diameter in a range from 0.007 inches (0.178 mm) to 0.047 inches (1.19 mm).

106. A ductal access device as in claim 98, further comprising: an infusion tube connected to the first port of the hub; and a collection tube connected to the second port of the hub.

107. A ductal access device as in claim 98, wherein the manifold has a volume in the range from 0.01 cc to 1.0 cc.

108. A ductal access device as in claim 98, wherein the first side port is spaced above the lower port by a distance less than 5 mm and the second side port is spaced above the first side port by a distance in the range from 0.10 mm to 5 mm.

109. A ductal access device as in claim 98, further comprising a dilator removably received in the hub and having a distal tip which is positionable through the access tube to extend from the distal end thereof.

110. A ductal access device as in claim 109, wherein the dilator has an outer

diameter of 0.024 inches (or 0.061 mm) or less.

111. A ductal access device as in claim 109, wherein the dilator is positionable through the hub manifold and into the lumen of the access tube.

112. A ductal access device as in claim 109, wherein the dilator is tapered.

113. A ductal access device as in claim 109, wherein a receiving portion of the hub for receiving the dilator comprises a water-tight seal.

114. A ductal access device as in claim 98, further comprising means on the access tube for positioning the distal end of the access tube distal to the ductal sphincter.

115. A ductal access device as in claim 114, wherein the positioning means comprises length indicia on the tube which permit a user to determine the depth to which the distal end of the tube has been introduced.

116. A ductal access device as in claim 114, wherein the positioning means comprises a stop element formed or attached to the tube, wherein the stop has dimensions which prevent further insertion of the tube into the duct and wherein the stop is positioned on the tube so that the distal tip will be located distal to the ductal sphincter when the device is fully inserted up to the stop.

117. A ductal access device as in claim 116, wherein the stop element comprises a collar affixed to or formed on an exterior surface of the tube.

118. A ductal access device as in claim 116, wherein the stop element comprises a hub attached to a proximal end of the tube, wherein the hub has a width which is greater than the diameter of the tube so that a shoulder is formed at a junction between the tube and the hub.

119. A ductal access device as in claim 98, further comprising means for anchoring the device to the breast.

120. A ductal access device as in claim 114, wherein the positioning means comprises a nob on the access tube having an increase diameter for anchoring the tube distal to a ductal sphincter once the nob has passed the sphincter and rests distal to it.

121. A ductal access system comprising: a ductal access device as in claim 98; and a container holding a premeasured volume of ductal wash fluid.

122. A ductal access system as in claim 121, wherein the container comprises a syringe for connection to the first side port.

123. A ducal access system as in claim 121, wherein the pre-measured volume is in the range from 2 ml to 100 ml.

124. A ductal access system as in claim 121, wherein the ductal access fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

125. A ductal access system as in claim 121, wherein the ductal access fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

126. A ductal access catheter comprising: a catheter body having a distal end and a proximal end and including at least a distal portion and a proximal portion; wherein the distal portion has a cross-sectional geometry which can be inserted through a ductal orifice into a ductal lumen of a human breast; wherein the proximal portion has a cross-sectional geometry which inhibits insertion through the ductal orifice

and into the ductal lumen; and wherein the catheter body has at least an infusion lumen and an collection lumen each of which has a distal port near a distal end of the distal portion and a proximal connector near a proximal end of the proximal portion.

127. A ductal access catheter as in claim 126, wherein the distal portion of the catheter body is stiffened over at least a part of its length to facilitate insertion through the ductal orifice and into the ductal lumen.

128. A ductal access catheter as in claim 127, wherein the stiffened distal portion of the catheter body has an average bending stiffness in the range from about 0.010 inch-lbs to about 0.50 inch-lbs.

129. A ductal access catheter as in claim 127, further comprising a stiffening member disposed in the distal portion of the catheter body.

130. A ductal access catheter as in claim 126, wherein the distal portion of the catheter body has a maximum width in the range from 0.008 inches (0.020 mm) to 0.035 inches (0.089 mm) and the proximal portion of the catheter body has a minimum width in the range from 0.010 inches (0.0254 mm) to 0.100 inches (0.254 mm).

131. A ductal access catheter as in claim 130, wherein the distal portion of the catheter body has a generally tubular structure with a diameter in the range from 0.008 inches (0.020 mm) to 0.035 inches (0.089 mm) and the proximal portion of the catheter body has a generally tubular structure with a diameter in the range from 0.030 inches (0.076 mm) to 0.10 inches (0.254 mm) and wherein the proximal diameter is greater than the distal diameter by at least 0.010 inches.

132. A ductal access catheter as in claim 126, wherein at least one of the distal collection port and the distal infusion portion are disposed on a side of the distal portion of the catheter body.

133. A ductal access catheter as in claim 132, wherein the distal collection port and the distal infusion port are both located on the side of the distal portion of the catheter body.

134. A ductal access catheter as in claim 133, wherein the distal collection port and the distal infusion port are axially aligned.

135. A ductal access catheter as in claim 133, wherein the distal collection port and the distal infusion port are axially spaced apart.

136. A ductal access catheter as in claim 133, wherein the catheter body includes an atraumatic distal tip.

137. A ductal access catheter as in claim 136, wherein the tip is composed of a soft polymeric material, has a diameter in the range from about 0.008 inches (0.020 mm) to about 0.035 inches (0.089 mm), and a length at least 0.25 cm.

138. A ductal access catheter comprising: a catheter body having a distal end and a proximal end and including at least a distal portion and a proximal portion; wherein the distal portion has a cross-sectional geometry which can be inserted through a ductal orifice into a ductal lumen of a human breast; wherein the distal portion of the catheter body is stiffened over at least a part of its length to facilitate insertion through the ductal orifice and into the ductal lumen; and wherein the catheter body has at least an infusion lumen and an collection lumen each of which has a distal port near a distal end of the distal portion and a proximal connector near a proximal end of the proximal connector.

139. A ductal access catheter as in claim 138, wherein the stiffened distal portion of the catheter body has an average bending stiffness in the range from about 0.010 inch-lbs to about 0.50 inch-lbs.

140. A ductal access catheter as in claim 138, wherein the proximal portion has a cross-sectional geometry which inhibits insertion through the ductal orifice and

into the ductal lumen.

141. A ductal access catheter comprising: a catheter body having a distal end and a proximal end and including at least a distal portion and a proximal portion; wherein the distal portion has a cross-sectional geometry which can be inserted through a ductal orifice into a ductal lumen of a human breast; and wherein the catheter body has at least an infusion lumen and an collection lumen each of which has a distal port near a distal end of the distal portion and a proximal connector near a proximal end of the proximal connector; and wherein the distal collection port and the distal infusion port are both located on the side of the distal portion of the catheter body.

142. A ductal access catheter as in claim 141, wherein the distal collection port and the distal infusion port are axially aligned.

143. A ductal access catheter as in claim 141, wherein the distal collection port and the distal infusion port are axially spaced apart.

144. A ductal access catheter as in claim 141, wherein the proximal portion has a cross-sectional geometry which inhibits insertion through the ductal orifice and into the ductal lumen.

145. A method for lavage of a ductal network in a human breast, said method comprising: providing a catheter as in claim 127; inserting the distal portion of the catheter through a ductal orifice and into a distal lumen of the ductal network; introducing a wash fluid through the infusion lumen into the ductal network; and withdrawing the wash fluid and substances borne by the wash fluid from the ductal network through the collection lumen.

146. A ductal access system comprising: a catheter as in claim 127, and instructions for use setting forth a method for lavage of a ductal network in a human breast including introducing a wash fluid through the infusion lumen into the ductal network and withdrawing the wash fluid and substances borne by the wash fluid from the ductal network through the collection lumen.

147. A device as in claim 52, further comprising a means for controlling a flow of fluid through the infusion lumen.

148. A device as in claim 52, further comprising a means for controlling a flow of fluid through the collection lumen.

149. A device as in claim 52, further comprising both a means for controlling a fluid flow through the infusion lumen and a means for controlling a fluid flow through the collection lumen.

150. A device as in claim 149, wherein the fluid control means comprise compressable lumens.

151. A device as in claim 149, wherein the fluid control means comprise stopcocks on each lumen.

152. A device as in claim 106, further comprising a means for controlling a flow of fluid through the infusion tube.

153. A device as in claim 106, further comprising a means for controlling a flow of fluid through the collection tube.

154. A device as in claim 106, further comprising both a means for controlling a fluid flow through the infusion lumen and a means for controlling a fluid flow through the collection lumen.

155. A device as in claim 154, wherein the fluid control means comprise compressable lumens.

156. A device as in claim 154, wherein the fluid control means comprise stopcocks on

each lumen.

157. A method for increasing an amount of fluid collectable from a milk duct of a breast of a mammal comprising administering an agent to a ductal lumen of a breast capable of maintaining or increasing the amount of collectable fluid in the ductal lumen, and collecting the fluid from the duct.

158. The method of claim 157, wherein the agent comprises an agent selected from the group consisting of a nonabsorbable agent, an oncotic agent and an osmotic agent.

159. The method of claim 157, wherein the agent is soluble.

160. The method of claim 157, wherein the agent comprises a molecule selected from the group consisting of a protein, a colloid, a sugar, and a polymer.

161. The method of claim 160, wherein the agent comprises a protein and the protein is selected from the group consisting of a binding protein and an antibody.

162. The method of claim 161, wherein the protein is a binding protein, and the binding protein comprises albumin.

163. The method of claim 157, wherein the agent comprises an agent selected from the group consisting of mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, albumin, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, and a synthetic colloid.

164. The method of claim 157, wherein administering comprises administering locally.

165. The method of claim 164, wherein administering locally comprises administering intraductally.

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TITLE: Method for differentiating breast ducts for cancer risk status

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INVENTOR-INFORMATION:

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US-CL-CURRENT: 600/363; 600/362

CLAIMS:

What is claimed is:

1. A method for differentiating a cancer risk status of milk ducts in a breast comprising: aspirating the nipple, and locating at least one ductal orifice that yields fluid upon aspiration; wherein a duct that yields fluid upon aspiration is at higher risk for cancer.

2. A method as in claim 1, further comprising accessing the ductal orifice that yields fluid.

3. A method as in claim 2, further comprising retrieving ductal contents from the accessed duct.

4. A method as in claim 1, wherein more than one duct yields fluid upon aspiration of the nipple.

5. A method as in claim 4, wherein each duct that yields fluid upon aspiration is accessed.

6. A method as in claim 5, further comprising retrieving ductal contents from an accessed duct.

7. A method as in claim 1, further comprising recording the location of the ductal orifice once identified by yield of fluid at the orifice.

8. A method as in claim 7, wherein recording comprises one or more of transcribing the relative location of the ductal orifice on a paper grid, taking a photograph, recording in real time on a digital screen the fluid yielding event and/or location of the ductal orifice that yielded fluid, and making a negative imprint on the nipple surface to identify the regions of the nipple that did not yield fluid.

9. A method as in claim 1, further comprising marking the ductal orifice upon yield of fluid at the orifice.

10. A method as in claim 9, wherein marking comprises making an identifiable mark with a pen or other labeling device to identify the spot comprising the ductal orifice at a later time.

11. A method as in claim 9, wherein marking comprises placing an element into the duct selected from the group consisting of a plug, tube, wire, thread, and suture.

12. A method as in claim 10, wherein the mark resides on the nipple surface in a range of time from a few hours to a few years.

13. A method as in claim 1, further comprising contacting a ductal orifice that yields fluid with a dilator in order to accomplish one or more of discerning the precise location of the orifice, discerning the orientation of the orifice, or enlarging the proximal area of the duct so as to facilitate subsequent cannulation of the duct.

14. A method for differentiating a cancer risk status of milk ducts in a breast comprising: aspirating the nipple, and locating at least one ductal orifice that yields fluid upon aspiration; wherein a duct that yields fluid upon aspiration is at higher risk for cancer; and collecting a bead of fluid at the nipple surface generated from aspiration and emerging from the fluid yielding duct and not mixed with fluid generated from any other duct on the nipple surface.

15. A method as in claim 14, further comprising analyzing the collected fluid of the duct yielding fluid separately from the fluid of any other duct yielding fluid.

16. A method as in claim 14, further comprising recording the location of the ductal orifice on the nipple surface once identified by yield of fluid.

17. A method as in claim 16, wherein recording comprises one or more of transcribing the relative location of the ductal orifice on a paper grid, taking a photograph, recording in real time on a digital screen the fluid yielding event and/or location of the ductal orifice that yielded fluid, and making a negative imprint on the nipple surface to identify the regions of the nipple that did not yield fluid.

18. A method as in claim 14, further comprising marking the ductal orifice upon yield of fluid at the orifice.

19. A method as in claim 18, wherein marking comprises making an identifiable mark with a pen or other labeling device to identify the spot comprising the ductal orifice at a later time.

20. A method as in claim 18, wherein marking comprises placing an element into the duct selected from the group consisting of a plug, tube, wire, thread, and suture.

21. A method as in claim 19, wherein the mark resides on the nipple surface in a range of time from a few hours to a few years.

22. A method as in claim 14, further comprising contacting a ductal orifice that yields fluid with a dilator in order to accomplish one or more of discerning the precise location of the orifice, discerning the orientation of the orifice, or enlarging the proximal area of the duct so as to facilitate subsequent cannulation of the duct.

23. A kit for differentiating a cancer risk status of milk ducts in a breast comprising a nipple aspiration device, a system to mark and/or record the location of a ductal orifice that yields fluid upon aspiration, and instructions for use of the kit to differentiate a cancer risk status of milk ducts in a breast by locating at least one ductal orifice that yields fluid upon aspiration.

24. A kit as in claim 23, further comprising a ductal access tool and further instructions to access the duct that yields fluid upon nipple aspiration.

25. A kit as in claim 23, wherein the system to mark and/or record the location of the ductal orifice that yields fluid upon aspiration comprises one or more of a pencil and graph paper, a camera, a marking tool, a digital recording and imaging device, a system to make a negative imprint on the nipple surface, and an element to place in the orifice to mark it.

26. A kit as in claim 24, further comprising a dilator.

27. A kit for differentiating a cancer risk status of milk ducts in a breast comprising a nipple aspiration device, a ductal access tool to access a duct through a ductal orifice that yields fluid upon nipple aspiration, and instructions for use of the kit to differentiate a cancer risk status of milk ducts in a breast by locating at least one ductal orifice that yields fluid upon nipple aspiration and access the duct through its orifice.

28. A kit as in claim 27, further comprising a dilator.

29. A kit for differentiating a cancer risk status of milk ducts in a breast comprising a nipple aspiration device, a tool to retrieve an emerging bead of fluid at a ductal orifice, and instructions for use of the kit to differentiate a cancer risk status of milk ducts in a breast by locating at least one ductal orifice that yields fluid upon nipple aspiration and instructions for collecting an emerging bead of fluid at the ductal orifice without mixing the collected fluid with any other fluid yielded from any other duct.

30. A kit as in claim 28, further comprising a dilator.

31. A method of maximizing the likelihood of ductal fluid migrating to the nipple surface upon nipple aspiration comprising: stimulating the breast and/or nipple surface prior to or during nipple aspiration.

32. A method as in claim 31, wherein stimulating comprises placing a wearable device in contact with the nipple surface.

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TITLE: Devices, methods and systems for collecting material from a breast duct

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CLAIMS:

What is claimed is:

1. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a wash fluid to the breast milk duct, wherein a volume of at least 2 ml is present within the duct for a preselected time; and collecting at least a portion of the introduced wash fluid from within the duct, wherein said portion carries the cellular material.

2. A method as in claim 1, wherein the preselected time is less than one second.

3. A method as in claim 1, wherein the preselected time is in the range from one second to one hour.

4. A method as in claim 1, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

5. A method as in claim 1, wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

6. A method as in claim 1, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

7. A method as in claim 1, further comprising separating cellular material from the collected fluid.

8. A method as in claim 7, further comprising examining the separated cellular material.

9. A method as in claim 1, wherein the cellular material is a substance selected from the group consisting of whole cells, cellular debris, proteins, nucleic acids, polypeptides, glycoproteins, lipids, fats, glycoproteins, small organic molecules, metabolites, and macromolecules.

10. A method as in claim 1, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

11. A method as in claim 1, wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

12. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a ductal access device having at least one lumen therethrough into a duct; introducing a wash fluid through the access device lumen into the milk duct, wherein a volume of at least 2 ml is present within the duct for a preselected time; and collecting at least a portion of the wash fluid from the duct through the lumen of the access device.

13. A method as in claim 12, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

14. A method as in claim 12, wherein introducing the ductal access device comprises positioning a distal end thereof distal to the ductal sphincter.

15. A method as in claim 12, wherein the access device has only a single lumen which extends into the duct.

16. A method as in claim 12, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

17. A methods as in claim 12, wherein the preselected time is less than one second.

18. A method as in claim 12, wherein the preselected time is in the range from one second to one hour.

19. A method as in claim 12, wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

20. A method as in claim 12, further comprising separating cellular material from the collected fluid.

21. A method as in claim 20, further comprising examining the separated cellular material.

22. A method as in claim 17, wherein the cellular material is a substance selected from the group consisting of whole cells, cellular debris, proteins, nucleic acids, polypeptides, glycoproteins, lipids, fats, glycoproteins, small organic molecules, metabolites, and macromolecules.

23. A method as in claim 12, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

24. A method as in claim 12, wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and

albuinin.

25. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a wash fluid to the breast milk duct, wherein the wash fluid is present within the duct for a preselected time; and collecting at least a portion of the introduced wash fluid from within the duct, wherein said portion carries the cellular material; wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

26. A method as in claim 25, wherein the volume of wash fluid is at least 2 ml.

27. A method as in claim 25, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

28. A method as in claim 25, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

29. A method as in claim 25, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

30. A method as in claim 25, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

31. A method as in claim 25, wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

32. A method as in claim 25, wherein the preselected time is less than one second.

33. A method as in claim 25, wherein the preselected time is in a range from one second to one hour.

34. A method as in claim 25, further comprising separating cellular material from the collected fluid.

35. A method as in claim 34, further comprising examining the separated cellular material.

36. A method as in claim 25, wherein the cellular material is a substance selected from the group consisiting of whole cells, cellular debris, nucleic acids, lipids, protein metabolites, small organic molecules, and macromolecules.

37. A method for obtaining cellular material from a human breast milk duct, said method comprising: introducing a ductal access device having at least one lumen therethrough into a duct; introducing a wash fluid through the access device lumen into the milk duct, wherein the wash fluid is present within the duct for a preselected time; and collecting at least a portion of the wash fluid from the duct through the lumen of the access device; wherein the wash fluid is introduced to a single breast milk duct and collected from the same breast milk duct without mixing with materials from other breast milk ducts.

38. A method as in claim 37, wherein the volume of wash fluid is at least 2 ml.

39. A method as in claim 37, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

40. A method as in claim 37, wherein the wash fluid is introduced to a volume of at least 2 ml prior to collecting any of wash fluid from the duct.

41. A method as in claim 37, wherein the preselected time is less than one second.

42. A method as in claim 37, wherein the preselected time is in a range from one second to one hour.

43. A method as in claim 37, further comprising massaging and squeezing the breast tissue after introducing the wash fluid but prior to and during collecting a portion of the wash fluid.

44. A method as in claim 37, wherein introducing the ductal access device comprises positioning a distal end thereof distal to the ductal sphincter.

45. A method as in claim 37 wherein the access device has only a single lumen which extends into the duct.

46. A method as in claim 37, further comprising separating cellular material from the collected fluid.

47. A method as in claim 46, further comprising examining the separated cellular material.

48. A method as in claim 37, wherein the cellular material is a substance selected from the group consisiting of whole cells, cellular debris, nucleic acids, lipids, protein metabolites, small organic molecules, and macromolecules.

49. A method as in claim 37, wherein the wash fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

50. A method as in claim wherein the wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

51. A kit comprising: a ductal access device; and instructions for use setting forth a method according to claim 12.

52. A ductal access device comprising: an access tube having a distal end, at least one lumen therethrough, and dimensions which permit introduction of the distal end through a ductal orifice and positioning a distal end thereof distal to the ductal sphincter of a human breast.

53. A ductal access device as in claim 52, further comprising means on the access tube for positioning the distal end distal to the ductal sphincter.

54. A ductal access device as in claim 53, wherein the positioning means comprises length indicia on the tube which permit a user to determine the depth to which the distal end of the tube has been introduced.

55. A ductal access device as in claim 53, wherein the positioning means comprises a stop element formed or attached to the tube, wherein the stop has dimensions which prevent further insertion of the tube into the duct and wherein the stop is positioned on the tube so that the distal tip will be located distal to the ductal sphincter when the device is fully inserted up to the stop.

56. A ductal access device as in claim 55, wherein the stop element comprises a collar affixed to or formed on an exterior surface of the tube.

57. A ductal access device as in claim 52, further comprising means for anchoring the device to the breast.

58. A ductal access device as in claim 52, further comprising a receiving portion comprising a water tight seal for receiving the dilator.

59. A ductal access device as in claim 55, wherein the stop element comprises a hub attached to a proximal end of the tube, wherein the hub has a width which is greater than the diameter of the tube so that a shoulder is formed at a junction between the tube and the hub.

60. A ductal access device as in claim 53, wherein the positioning means comprises a nob on the access tube having an increase diameter for anchoring the tube distal to the ductal sphincter once the nob has passed the sphincter and rests distal to it.

61. A ductal access device as in claim 52, wherein the access tube has an outer diameter of 0.05 inches or 1.27 mm or less.

62. A ductal access device as in claim 52, wherein the access tube has an outer diameter of 0.010 inches (or 0.254 mm) or greater.

63. A ductal access device as in claim 53, wherein the outer diameter is in the range from 0.010 inches or 0.254 mm to 0.050 inches or 1.27 mm.

64. A ductal access device as in claim 52, wherein the access tube has a lumen diameter 0.007 inches (or 0.178 mm) or greater.

65. A ductal access device as in claim 52, wherein the access tube has a lumen diameter in the range from 0.007inches or 0.178 mm to 0.047 inches or 1.19 mm.

66. A ductal access device as in claim 52, further comprising: an infusion connector providing a fluid flow path into the lumen of the tube; and a collection connector providing a fluid outlet path from the lumen of the tube, said infusion and collection connectors being isolated from each other so that the fluid may be infused through the infusion connector and simultaneously removed through the collection connector.

67. A ductal access device as in claim 52, further comprising a dilator removably received in the access tube and having a distal tip which is positionable through the access tube to extend from the distal end thereof.

68. A ductal access device as in claim 67, wherein the dilator has an outer diameter of 0.024 inches (or 0.61 mm) or less.

69. A ductal access device as in claim 67, wherein the dilator is tapered.

70. A ductal access device as in claim 67, wherein a receiving portion of the device for receiving the dilator comprises a water-tight seal.

71. A ductal access system comprising: a ductal access device as in claim 52; and a container holding a premeasured volume of ductal wash fluid.

72. A ductal access system as in claim 71, wherein the container comprises a syringe for connection to the first side port.

73. A ducal access system as in claim 71, wherein the pre-measured volume is in the range from 2 ml to 100 ml.

74. A ductal access system as in claim 71, wherein the ductal access fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

75. A ductal access system as in claim 71, wherein the ductal access fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

76. A ductal access device comprising: an access tube having a distal end, a single lumen therethrough, and dimensions which permit introduction of the distal end through a ductal orifice and positioning a distal end thereof distal to the ductal sphincter; an infusion connector providing a fluid flow path into the lumen of the access tube; and a collection connector providing a fluid outlet path from the lumen of the access tube, said infusion and collection connectors being isolated from each other so that fluid may be infused through the infusion connector and simultaneously removed through the collection connector.

77. A ductal access device as in claim 76, wherein the tube has an outer diameter of 0.010 inches or 0.254 mm or greater.

78. A ductal access device as in claim 76, wherein the tube has an outer diameter of 0.050 inches or 1.27 mm or less.

79. A ductal access device as in claim 77, wherein the outer diameter is in the range from 0.010 inches or 0.254 mm to 0.050 inches or 1.27 mm.

80. A ductal access device as in claim 76, wherein the access tube has a lumen diameter 0.007 inches or 0.178 mm or greater.

81. A ductal access device as in claim 79, wherein the access tube has a lumen diameter in the range from 0.007 inches or 0.178 mm to 0.047 inches or 1.1.9 mm.

82. A ductal access device as in claim 76, further comprising means on the access tube positioning a distal end thereof distal to the ductal sphincter.

83. A ductal access device as in claim 82, wherein the positioning means comprises length indicia on the tube which permit a user to determine the depth to which the distal end of the tube has been introduced.

84. A ductal access device as in claim 82, wherein the positioning means comprises a stop element formed or attached to the tube, wherein the stop has dimensions which prevent further insertion of the tube into the duct and wherein the stop is positioned on the tube so that a distal end of the distal tip is positioned thereof distal to the ductal sphincter.

85. A ductal access device as in claim 84, wherein the stop element comprises a collar affixed to or formed on an exterior surface of the tube.

86. A ductal access device as in claim 84, wherein the stop element comprises a hub attached to a proximal end of the tube, wherein the hub has a width which is greater than the diameter of the tube so that a shoulder is formed at a junction between the tube and the hub.

87. A ductal access device as in claim 82, wherein the positioning means comprises a nob on the access tube having an increase diameter for anchoring the tube distal to the ductal sphincter once the nob has passed the sphincter and rests distal to it.

88. A ductal access device as in claim 76, further comprising means for anchoring the device to the breast.

89. A ductal access device as in claim 76, further comprising a dilator removably received in the access tube and having a distal tip which is positionable through the access tube to extend from the distal end thereof.

90. A ductal access device as in claim 89, wherein the dilator has an outer diameter of 0.024 inches (or 0.061 mm) or less.

91. A ductal access device as in claim 89, wherein the dilator is tapered.

92. A ductal access device as in claim 89, wherein a receiving portion of the device for receiving the dilator comprises a water-tight seal.

93. A ductal access system comprising: a ductal access device as in claim 76; and a

container holding a premeasured volume of ductal wash fluid.

94. A ductal access system as in claim 93, wherein the ductal wash fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

95. A ductal access system as in claim 93, wherein the container comprises a syringe for connection to the first side port.

96. A ductal access system as in claim 93, wherein the premeasured volume is in the range from 2 ml to 100 ml.

97. A ductal access system as in claim 93, wherein the ductal access fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

98. A ductal access device comprising: a hub having an internal elongate manifold, a lower port at a bottom of the manifold, and first and second side ports spaced above the lower port; and an access tube having a distal end, a proximal end, a lumen therethrough, and dimensions which permit introduction of the distal end through a ductal orifice and a positioning a distal end thereof distal to the ductal sphincter of the human breast, wherein the proximal end of the tube is attached to the lower port of the hub.

99. A ductal access device as in claim 98, wherein the first and second side ports are at the same level relative to the lower port.

100. A ductal access device as in claim 98, wherein the first side port is below the second side port.

101. A ductal access device as in claim 98, wherein the access tube has an outer diameter of 0.010 inches or 0.245 mm or greater.

102. A ductal access device as in claim 98, wherein the access tube has an outer diameter of 0.50 inches or 1.27 mm or less.

103. A ductal access device as in claim 101, wherein the outer diameter is in the range from 0.010 inches or 0.245 mm to 0.050 inches or 1.27 mm.

104. A ductal access device as in claim 103, wherein the access tube has a lumen diameter 0.007 inches (0.178 mm) or greater.

105. A ductal access device as in claim 103, wherein the access tube has a lumen diameter in a range from 0.007 inches (0.178 mm) to 0.047 inches (1.19 mm).

106. A ductal access device as in claim 98, further comprising: an infusion tube connected to the first port of the hub; and a collection tube connected to the second port of the hub.

107. A ductal access device as in claim 98, wherein the manifold has a volume in the range from 0.01 cc to 1.0 cc.

108. A ductal access device as in claim 98, wherein the first side port is spaced above the lower port by a distance less than 5 mm and the second side port is spaced above the first side port by a distance in the range from 0.10 mm to 5 mm.

109. A ductal access device as in claim 98, further comprising a dilator removably received in the hub and having a distal tip which is positionable through the access tube to extend from the distal end thereof.

110. A ductal access device as in claim 109, wherein the dilator has an outer

diameter of 0.024 inches (or 0.061 mm) or less.

111. A ductal access device as in claim 109, wherein the dilator is positionable through the hub manifold and into the lumen of the access tube.

112. A ductal access device as in claim 109, wherein the dilator is tapered.

113. A ductal access device as in claim 109, wherein a receiving portion of the hub for receiving the dilator comprises a water-tight seal.

114. A ductal access device as in claim 98, further comprising means on the access tube for positioning the distal end of the access tube distal to the ductal sphincter.

115. A ductal access device as in claim 114, wherein the positioning means comprises length indicia on the tube which permit a user to determine the depth to which the distal end of the tube has been introduced.

116. A ductal access device as in claim 114, wherein the positioning means comprises a stop element formed or attached to the tube, wherein the stop has dimensions which prevent further insertion of the tube into the duct and wherein the stop is positioned on the tube so that the distal tip will be located distal to the ductal sphincter when the device is fully inserted up to the stop.

117. A ductal access device as in claim 116, wherein the stop element comprises a collar affixed to or formed on an exterior surface of the tube.

118. A ductal access device as in claim 116, wherein the stop element comprises a hub attached to a proximal end of the tube, wherein the hub has a width which is greater than the diameter of the tube so that a shoulder is formed at a junction between the tube and the hub.

119. A ductal access device as in claim 98, further comprising means for anchoring the device to the breast.

120. A ductal access device as in claim 114, wherein the positioning means comprises a nob on the access tube having an increase diameter for anchoring the tube distal to a ductal sphincter once the nob has passed the sphincter and rests distal to it.

121. A ductal access system comprising: a ductal access device as in claim 98; and a container holding a premeasured volume of ductal wash fluid.

122. A ductal access system as in claim 121, wherein the container comprises a syringe for connection to the first side port.

123. A ducal access system as in claim 121, wherein the pre-measured volume is in the range from 2 ml to 100 ml.

124. A ductal access system as in claim 121, wherein the ductal access fluid is selected from the group consisting of saline, phosphate buffered saline, a nonabsorbable fluid, an isotonic solution, an osmotic solution, a hypotonic solution, and a hypertonic solution.

125. A ductal access system as in claim 121, wherein the ductal access fluid is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, and albumin.

126. A ductal access catheter comprising: a catheter body having a distal end and a proximal end and including at least a distal portion and a proximal portion; wherein the distal portion has a cross-sectional geometry which can be inserted through a ductal orifice into a ductal lumen of a human breast; wherein the proximal portion has a cross-sectional geometry which inhibits insertion through the ductal orifice

and into the ductal lumen; and wherein the catheter body has at least an infusion lumen and an collection lumen each of which has a distal port near a distal end of the distal portion and a proximal connector near a proximal end of the proximal portion.

127. A ductal access catheter as in claim 126, wherein the distal portion of the catheter body is stiffened over at least a part of its length to facilitate insertion through the ductal orifice and into the ductal lumen.

128. A ductal access catheter as in claim 127, wherein the stiffened distal portion of the catheter body has an average bending stiffness in the range from about 0.010 inch-lbs to about 0.50 inch-lbs.

129. A ductal access catheter as in claim 127, further comprising a stiffening member disposed in the distal portion of the catheter body.

130. A ductal access catheter as in claim 126, wherein the distal portion of the catheter body has a maximum width in the range from 0.008 inches (0.020 mm) to 0.035 inches (0.089 mm) and the proximal portion of the catheter body has a minimum width in the range from 0.010 inches (0.0254 mm) to 0.100 inches (0.254 mm).

131. A ductal access catheter as in claim 130, wherein the distal portion of the catheter body has a generally tubular structure with a diameter in the range from 0.008 inches (0.020 mm) to 0.035 inches (0.089 mm) and the proximal portion of the catheter body has a generally tubular structure with a diameter in the range from 0.030 inches (0.076 mm) to 0.10 inches (0.254 mm) and wherein the proximal diameter is greater than the distal diameter by at least 0.010 inches.

132. A ductal access catheter as in claim 126, wherein at least one of the distal collection port and the distal infusion portion are disposed on a side of the distal portion of the catheter body.

133. A ductal access catheter as in claim 132, wherein the distal collection port and the distal infusion port are both located on the side of the distal portion of the catheter body.

134. A ductal access catheter as in claim 133, wherein the distal collection port and the distal infusion port are axially aligned.

135. A ductal access catheter as in claim 133, wherein the distal collection port and the distal infusion port are axially spaced apart.

136. A ductal access catheter as in claim 133, wherein the catheter body includes an atraumatic distal tip.

137. A ductal access catheter as in claim 136, wherein the tip is composed of a soft polymeric material, has a diameter in the range from about 0.008 inches (0.020 mm) to about 0.035 inches (0.089 mm), and a length at least 0.25 cm.

138. A ductal access catheter comprising: a catheter body having a distal end and a proximal end and including at least a distal portion and a proximal portion; wherein the distal portion has a cross-sectional geometry which can be inserted through a ductal orifice into a ductal lumen of a human breast; wherein the distal portion of the catheter body is stiffened over at least a part of its length to facilitate insertion through the ductal orifice and into the ductal lumen; and wherein the catheter body has at least an infusion lumen and an collection lumen each of which has a distal port near a distal end of the distal portion and a proximal connector near a proximal end of the proximal connector.

139. A ductal access catheter as in claim 138, wherein the stiffened distal portion of the catheter body has an average bending stiffness in the range from about 0.010 inch-lbs to about 0.50 inch-lbs.

140. A ductal access catheter as in claim 138, wherein the proximal portion has a cross-sectional geometry which inhibits insertion through the ductal orifice and

into the ductal lumen.

141. A ductal access catheter comprising: a catheter body having a distal end and a proximal end and including at least a distal portion and a proximal portion; wherein the distal portion has a cross-sectional geometry which can be inserted through a ductal orifice into a ductal lumen of a human breast; and wherein the catheter body has at least an infusion lumen and an collection lumen each of which has a distal port near a distal end of the distal portion and a proximal connector near a proximal end of the proximal connector; and wherein the distal collection port and the distal infusion port are both located on the side of the distal portion of the catheter body.

142. A ductal access catheter as in claim 141, wherein the distal collection port and the distal infusion port are axially aligned.

143. A ductal access catheter as in claim 141, wherein the distal collection port and the distal infusion port are axially spaced apart.

144. A ductal access catheter as in claim 141, wherein the proximal portion has a cross-sectional geometry which inhibits insertion through the ductal orifice and into the ductal lumen.

145. A method for lavage of a ductal network in a human breast, said method comprising: providing a catheter as in claim 127; inserting the distal portion of the catheter through a ductal orifice and into a distal lumen of the ductal network; introducing a wash fluid through the infusion lumen into the ductal network; and withdrawing the wash fluid and substances borne by the wash fluid from the ductal network through the collection lumen.

146. A ductal access system comprising: a catheter as in claim 127, and instructions for use setting forth a method for lavage of a ductal network in a human breast including introducing a wash fluid through the infusion lumen into the ductal network and withdrawing the wash fluid and substances borne by the wash fluid from the ductal network through the collection lumen.

147. A device as in claim 52, further comprising a means for controlling a flow of fluid through the infusion lumen.

148. A device as in claim 52, further comprising a means for controlling a flow of fluid through the collection lumen.

149. A device as in claim 52, further comprising both a means for controlling a fluid flow through the infusion lumen and a means for controlling a fluid flow through the collection lumen.

150. A device as in claim 149, wherein the fluid control means comprise compressable lumens.

151. A device as in claim 149, wherein the fluid control means comprise stopcocks on each lumen.

152. A device as in claim 106, further comprising a means for controlling a flow of fluid through the infusion tube.

153. A device as in claim 106, further comprising a means for controlling a flow of fluid through the collection tube.

154. A device as in claim 106, further comprising both a means for controlling a fluid flow through the infusion lumen and a means for controlling a fluid flow through the collection lumen.

155. A device as in claim 154, wherein the fluid control means comprise compressable lumens.

156. A device as in claim 154, wherein the fluid control means comprise stopcocks on

each lumen.

157. A method for increasing an amount of fluid collectable from a milk duct of a breast of a mammal comprising administering an agent to a ductal lumen of a breast capable of maintaining or increasing the amount of collectable fluid in the ductal lumen, and collecting the fluid from the duct.

158. The method of claim 157, wherein the agent comprises an agent selected from the group consisting of a nonabsorbable agent, an oncotic agent and an osmotic agent.

159. The method of claim 157, wherein the agent is soluble.

160. The method of claim 157, wherein the agent comprises a molecule selected from the group consisting of a protein, a colloid, a sugar, and a polymer.

161. The method of claim 160, wherein the agent comprises a protein and the protein is selected from the group consisting of a binding protein and an antibody.

162. The method of claim 161, wherein the protein is a binding protein, and the binding protein comprises albumin.

163. The method of claim 157, wherein the agent comprises an agent selected from the group consisting of mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, albumin, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, and a synthetic colloid.

164. The method of claim 157, wherein administering comprises administering locally.

165. The method of claim 164, wherein administering locally comprises administering intraductally.

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L18: Entry 17 of 34 File: PGPB Jan 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020013539
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020013539 A1

TITLE: Methods and devices for diagnosis of precancer and cancer in breast milk ducts

PUBLICATION-DATE: January 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	

US-CL-CURRENT: 600/573

CLAIMS:

What is claimed is:

1. A device for collection of breast duct fluid and detection of breast cancer or precancer comprising: a probe of a diameter sufficiently small to penetrate a breast duct having a distal portion capable of contacting an interior lumen of a breast duct, wherein said distal portion can contact and retrieve a sufficient sample of the breast duct fluid for analysis, said probe unattached to a fluid source or lumen.

2. A device as in claim 1, wherein the distal portion comprises an absorbent material that can absorb breast duct fluid.

3. A device as in claim 1, wherein the distal portion comprises a collection portion that can collect the breast duct fluid it contacts.

4. A device as in claim 3, wherein the collection portion is tubular.

5. A device as in claim 3, wherein the collection portion extends some of the distance of the probe.

6. A device as in claim 1, wherein the distal portion comprises a surface having molecules affixed that bind an agent in the ductal fluid it contacts.

7. A device as in claim 1, wherein the distal portion comprises a means to measure a quality of the ductal fluid in situ.

8. A device as in claim 7, wherein the quality comprises an indicia selected from the group consisting of cell size, cell density, nuclear size, nucleoli size, and chromatin coarseness.

9. A device as in claim 1, wherein the distal portion comprises a MEMS capable of detecting in situ a quality of the ductal fluid.

10. A device as in claim 9, wherein the quality comprises a marker.

11. A device as in claim 1, further comprising a coating of an anesthetic on the exterior of the probe.

12. A device as in claim 1, wherein the probe is rigid before entry into the breast duct, and flexible upon residence in the duct.

13. A device as in claim 1, wherein the probe comprises a shape memory material.

14. A method of collection and analysis of breast duct fluid and detection of breast cancer or precancer comprising: inserting a probe comprising a distal portion that can attract or collect breast duct fluid and contents; and collecting a sample of ductal fluid into the distal portion.

15. A method as in claim 14, further comprising analyzing the sample of ductal fluid collected by the distal portion of the probe.

16. A method as in claim 14, further comprising removing the probe from the breast duct and analyzing the sample of ductal fluid collected or attracted by the distal portion.

17. A method as in claim 14, wherein analyzing comprises contacting the distal portion comprising ductal fluid with a reagent.

18. A method as in claim 14, wherein analyzing comprises cytological analysis of ductal epithelial cells.

19. A method as in claim 14, wherein analyzing comprises detection of a marker.

20. A method as in claim 14, wherein analyzing comprises measuring a quality of the ductal fluid or ductal cells in situ.

21. A method as in claim 14, wherein collecting comprises a waiting period with the probe in the duct for a period of time in a range from about a few seconds to a few weeks.

22. A system of collection and analysis of breast duct fluid and detection of breast cancer or precancer comprising: a device comprising a probe for accessing a breast duct having a distal portion for collecting or attracting ductal fluid and/or ductal cells; reagents for contacting the distal portion for detection of a marker or analysis of the ductal fluid sample, and instructions for use of the system to diagnose breast cancer or precancer in a breast duct.

23. An article for collection of breast duct fluid and detection of breast cancer or precancer comprising: a receiving unit of a sufficient dimension to isolate a breast duct opening on a nipple surface, wherein said unit can contact a bead of ductal fluid on the nipple surface at the ductal orifice after nipple aspiration of said nipple.

24. The article as in claim 23, wherein the unit can absorb the aspirated ductal fluid from the nipple surface for analysis.

25. A method of collection and analysis of breast duct fluid and detection of breast cancer or precancer comprising: contracting a ductal orifice having a bead of ductal fluid on a nipple surface with a receiving unit of a sufficient dimension to isolate the ductal orifice, whereupon said unit absorbs the ductal fluid for analysis.

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L18: Entry 14 of 34 File: PGPB Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037265
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020037265 A1

TITLE: Preparation for breast duct fluid collection

PUBLICATION-DATE: March 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	
Patel, Tina	San Carlos	CA	US	

US-CL-CURRENT: 424/70.1

CLAIMS:

What is claimed is:

1. A composition to contact a breast nipple and to prepare a breast for ductal fluid collection comprising, in bioactive amounts, two or more of the following: an anesthetic agent, a detergent, an exfoliating agent, an antiseptic agent, a dekeratinyzing agent, an orifice-dilating agent, a vaso-dilator, a muscle-relaxing agent, muscle-constricting agent, a lactation-stimulating agent, a secretion-stimulating agent, a sphincter-relaxer, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice.

2. A method of preparing a breast for ductal fluid collection comprising: contacting the nipple surface with a composition comprising an anesthetic and one or more of a detergent, an exfoliating agent, an antiseptic agent, a dekeratinyzing agent, an orifice-dilating agent, a vaso-dilator, a muscle-relaxing agent, a muscle-constricting agent, a lactation-stimulating agent, a secretion-stimulating agent, a sphincter-relaxer, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice for sufficient time to allow the composition to take effect on the nipple surface.

3. A method of preparing a breast duct for access and ductal fluid collection comprising: contacting a ductal orifice with a tip of a ductal access tool coated with a composition comprising one or more of an anesthetic, a detergent, an exfoliating agent, an antiseptic agent, a dekeratinyzing agent, an orifice-dilating agent, a vaso-dilator, a muscle-relaxing agent, a muscle-constricting agent, a lactation-stimulating agent, a secretion-stimulating agent, a sphincter-relaxer, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice.

4. A method of preparing a breast duct for access and ductal fluid collection comprising: contacting a ductal orifice with a tip of a ductal access tool coated with a composition comprising one or more of an anesthetic, a detergent, an exfoliating agent, an antiseptic agent, a dekeratinizing agent, an orifice-dilating

agent, a vaso-dilator, a muscle-relaxing agent, a muscle-constricting agent, a lactation-stimulating agent, a secretion-stimulating agent, a sphincter-relaxer, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice; and infusing a solution comprising an anesthetic into the duct through a lumen of the ductal access tool.

5. A method of preparing a breast duct for access and ductal fluid collection comprising infusing a solution comprising an anesthetic and one or more of an oncotic agent, an osmotic agent, oxytocin, prolactin, a ductal orifice-dilating agent, a vaso-dilator, a vaso-constricter, a muscle-relaxant, a muscle-constricter, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice.

6. A system comprising: an aliquot of a bioactive composition comprising a mixture of one or more of an anesthetic, a detergent, an exfoliating agent, an antiseptic agent, a dekeratinizing agent, an orifice-dilating agent, a vaso-dilator, a muscle-relaxing agent, a muscle-constricting agent, a lactation-stimulating agent, a secretion-stimulating agent, a sphincter-relaxer, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice, in a formulation to contact a nipple surface.

7. A system of claim 6, wherein the formulation comprises a powder, a viscous semi-liquid, a foam, a gel, a liquid, or a gas.

8. A system as in claim 6, further comprising a pad of a geometry to circumscribe a breast nipple to enclose a bioactive agent in contact with a nipple surface and cover the nipple surface for sufficient time for the bioactive agent to act on the nipple surface.

9. A system comprising a ductal access tool and a composition of a formulation capable of coating a tip of the tool to contact a ductal orifice, said composition comprising one or more of an anesthetic, a detergent, an exfoliating agent, an antiseptic agent, a dekeratinizing agent, an orifice-dilating agent, a vaso-dilator, a muscle-relaxing agent, a muscle-constricting agent, a lactation-stimulating agent, a secretion-stimulating agent, a sphincter-relaxer, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice.

10. A system comprising a ductal access tool preloaded with a solution comprising an anesthetic for infusion into an accessed breast duct and a composition of a formulation capable of coating a tip of the tool comprising one or more of an anesthetic, a detergent, an exfoliating agent, an antiseptic agent, a dekeratinizing agent, an orifice-dilating agent, a vaso-dilator, a muscle-relaxing agent, a muscle-constricting agent, a lactation-stimulating agent, a secretion-stimulating agent, a sphincter-relaxer, an anti-ischemic agent, a beta-blocker, a calcium channel blocker, a dye or stain to mark the nipple surface excluding ductal orifices, a dye or stain to mark a perimeter of a ductal orifice, and a dye or stain to mark a ductal orifice.

11. A method of preparing a patient for a breast duct fluid collection comprising one or more of applying acupuncture, directing meditation, playing music, applying heat to the breast, warming a room where the patient waits, warming a table or chair where the patient lies or sits, covering the patient with a warm blanket.

L18: Entry 11 of 34 File: PGPB Aug 15, 2002

PGPUB-DOCUMENT-NUMBER: 20020110609
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020110609 A1

TITLE: Increasing retrievable fluid from a breast duct

PUBLICATION-DATE: August 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	

US-CL-CURRENT: 424/764; 514/2, 514/23, 514/53, 514/54, 514/58, 514/60

CLAIMS:

What is claimed is:

1. A method for preparing for intraductal retrieval of fluid, cells and/or other material from a breast duct of a patient, comprising: administering an agent to the patient that increases retrievable fluid from a breast duct.

2. A method as in claim 1, wherein administering is accomplished by a mode selected from the group consisting of administering the agent intraductally, administering the agent systemically, and administering the agent topically.

3. A method as in claim 2, wherein the agent is administered intraductally to a breast duct, and the agent is selected from the group consisting of saline, phosphate buffered saline (PBS), an isotonic solution, a hypotonic solution, a buffered solution, a solution having a pH range of human tissue, blood or sera, a solution having a slightly acid pH, a solution having a slightly basic pH, and a nonabsorbable biocompatable solution.

4. A method as in claim 2, wherein the agent is administered systemically and comprises an agent selected from the group consisting of a hormone, oxytocin, prolactin, a breast duct secretion inducing factor, a natural herb or extract from a natural herb, silymarin, a growth factor, a vitamin, a protein, a muscle relaxant, and a small organic molecule.

5. A method as in claim 2, wherein the agent is administered intraductally to a breast duct, and the agent is selected from the group consisting of a protein, a colloid, a sugar, a polymer, mannitol, sorbitol, glucose, glycerol, sucrose, raffinose, fructose, lactulose, sodium chloride, polyethyleneglycol (PEG), maltodextrin, dextran (e.g. dextran 70), hydroxyethyl starch, fluid gelatin, a synthetic colloid, an antibody, a binding protein, albumin, a hormone, a breast duct secretion inducing factor, a natural herb or extract from a natural herb, silymarin, a surfactant, a growth factor, oxytocin, prolactin, a small organic molecule, a muscle relaxant, a ductal orifice dilator, and an agent that increases fluid secretion from a breast duct epithelium.

6. A method as in claim 2, wherein the agent is intraductally administered and the agent is in a state selected from the group consisting of a non-liquid, a gel, an emulsion, a gas and a semi-solid.

7. A method as in claim 2, wherein the agent is intraductally administered agent and the agent comprises a carbonated fluid comprising super oxygenated fluid that is colder than room temperature before intraductal administration.

8. A method as in claim 1, further comprising collecting a portion of the increased breast duct fluid from a breast duct.

9. A method as in claim 8, wherein collecting comprises accessing a breast duct with a device and withdrawing a portion of the increased ductal fluid into the device.

10. A method as in claim 8, further comprising analyzing one or more of cells, fluid or other material in the breast duct after the retrievable fluid has been increased and a portion of it has been collected.

11. A method as in claim 10, wherein the step of analyzing comprises identifying a marker of a breast condition.

12. A method of collecting ductal fluid from a breast duct having artificially increased retrievable ductal fluid comprising accessing a breast duct with a device and withdrawing a portion of the ductal fluid into the device.

13. A method as in claim 12, wherein withdrawn ductal fluid comprises a plurality of ductal epithelial cells.

14. A method for increasing a retrievable cell amount in a breast duct comprising inducing cell sloughing within the duct by applying vibration to the duct.

15. A method as in claim 1 or claim 12 further comprising increasing a retrievable cell amount in a breast duct comprising inducing cell sloughing within the duct by applying vibration to the duct.

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L18: Entry 10 of 34 File: PGPB Sep 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020133151
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020133151 A1

TITLE: Methods and systems for treating breast tissue

PUBLICATION-DATE: September 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Love, Susan	Pacific Palisades	CA	US	
O'Leary, Shawn	Mission Viejo	CA	US	

US-CL-CURRENT: 606/41

CLAIMS:

What is claimed is:

1. A method for treating a breast duct of a patient, said method comprising the steps of: systemically introducing an agent into a patient targeted for treatment, said agent being sensitive to at least one form of energy; and transferring said at least one form of energy within said breast duct to the agent in the duct in an amount sufficient to disrupt the agent whereupon the agent acts on target cells lining the breast duct.

2. The method of claim 1 further comprising a step of introducing a tool into said breast duct through a ductal opening; and wherein said transferring step includes transferring said energy from said introduced tool to said agent.

3. The method of claim 1 wherein said target cells include benign cells and at least one of the following types of cells: cancerous and precancerous cells.

4. The method of claim 1 wherein said at least one form of energy is selected from the group consisting of light energy, electrical energy, electromagnetic energy, radiation energy, and vibrational energy.

5. The method of claim 1 wherein said agent contacts substantially all of a ductal network of said breast duct.

6. The method of claim 1 further including the step of identifying a portion of the duct to be treated; and wherein said transferring step includes transferring energy to only said portion of said duct to be treated.

7. The method of claim 1 further including the step of said agent ablating the target cells lining the breast duct.

8. The method of claim 1 further including the step of said agent inhibiting proliferation of the target cells lining the breast duct.

9. The method of claim 1 further including the step of said agent acting prophylactically on the target cells lining said breast duct.

10. The method of claim 1 wherein said agent comprises a photoactive agent.

11. The method of claim 4 wherein said radiation energy includes nuclear energy.

12. A method for treating a breast duct of a patient, said method comprising the steps of: systemically introducing an agent into a patient targeted for treatment, said agent being sensitive to at least one form of energy; introducing an energy delivering tool into the breast duct; and transferring said at least one form of energy from said tool to said agent in the duct in an amount sufficient to disrupt the agent whereupon the agent acts on target cells lining the breast duct, said target cells including benign cells and at least one of the following types of cells: cancerous and precancerous cells.

13. The method of claim 12 wherein said at least one form of energy is selected from the group consisting of light energy, electrical energy, electromagnetic energy, radiation energy and vibrational energy.

14. The method of claim 12 wherein said agent contacts substantially all of a ductal network of said breast duct.

15. The method of claim 12 further including the step of identifying a portion of the duct to be treated; and wherein said transferring step includes transferring energy to only said portion of said duct to be treated.

16. The method of claim 12 further including the step of said agent ablating the target cells lining the breast duct.

17. The method of claim 12 further including the step of said agent inhibiting proliferation of the target cells lining the breast duct.

18. The method of claim 12 further including the step of said agent acting prophylactically on the target cells lining said breast duct.

19. The method of claim 12 wherein said agent comprises a photoactive agent.

20. The method of claim 13 wherein said radiation energy includes nuclear energy.

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L18: Entry 8 of 34 File: PGPB Nov 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020169391
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020169391 A1

TITLE: Devices, methods and systems for collecting material from a breast duct

PUBLICATION-DATE: November 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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US-CL-CURRENT: 600/562; 435/7.23, 600/573, 604/28

CLAIMS:

What is claimed is:

1. A device for accessing a mammalian duct and collecting cellular material from within the duct, said device comprising: a catheter for being positioned within the duct, said catheter having a proximal end and a distal end, said distal end including an opening for delivering lavage fluid within the duct and receiving cellular material from within the duct; a manifold hub in fluid communication with the catheter, said manifold hub comprising a distal end having a first port that is axially aligned with an internal lumen of the catheter, a second port positioned within the hub for infusing fluids into said hub and a third port positioned within the hub for collecting fluid from within the hub.

2. The device according to claim 1 wherein said manifold hub includes at least one sidewall that extends parallel to a longitudinal axis of the device, said at least one sidewall includes the infusion port and the collection port.

3. The device according to claim 2 wherein said infusion port and collection port are aligned with each other along the at least one sidewall of the hub.

4. The device according to claim 3 wherein the infusion port is positioned proximate the first port relative to said collection port.

5. The device according to claim 3 wherein the collection port is positioned between the infusion port and a proximal end of the hub.

6. The device according to claim 2 wherein said hub has a substantially circular cross section, and said infusion port and collection port are circumferentially spaced from each other around the hub.

7. The device according to claim 1 further including an infusion line connected to the infusion port and a collection line connected to the collection port.

8. The device according to claim 7 further including a fluid infusing member removably secured to a terminal end of the infusion line for delivering fluid to the infusion line and the hub.

9. The device according to claim 8 wherein said infusing member comprises a syringe.

10. The device according to claim 7 further including a collecting member removably secured to a terminal end of the collection line.

11. The device according to claim 10 wherein said collecting member comprises a syringe.

12. The device according to claim 1 wherein the distal opening of the catheter is capable of being moved between a closed position and an open position.

13. The device according to claim 12 further including a mechanism for moving the distal catheter opening between the open and closed positions.

14. The device according to claim 13 wherein said mechanism includes a wire extending between the proximal and distal ends of the catheter.

15. The device according to claim 12 wherein said distal end of the catheter is formed of a shape memory material that opens in response to the application of a stimulus.

16. The device according to claim 15 wherein said stimulus includes heat or electric current.

17. The device according to claim 15 wherein said shape memory material is Nitinol.

18. The device according to claim 12 wherein the distal end has a larger opening than the proximal end of the catheter when the distal end is in the open position.

19. The device according to claim 1 further including a guide member for introducing the catheter into the duct.

20. The device according to claim 19 wherein the guide member includes a dilator having a tapered distal end.

21. The device according to claim 20 wherein the distal end of the dilator includes at least one opening for receiving a medicament.

22. The device according to claim 21 wherein the medicament is lidocane.

23. The device according to claim 1 wherein the distal end of the manifold hub is removably secured within the catheter.

24. The device according to claim 23 wherein the distal end of the manifold hub forms a luer lock connection with the catheter.

25. A ductal access device comprising a first elongated member for positioning within a breast duct, said first member comprising an internal lumen, and a manifold hub removably secured to said first member and being in fluid communication with a proximal end of the first elongated member.

26. The device according to claim 25 wherein said manifold hub includes a first opening that is axially aligned with the internal lumen of the elongated member.

27. The device according to claim 26 wherein said first opening is located at a distal end of the hub that is secured to said elongated member.

28. The device according to claim 27 wherein said manifold hub includes a sidewall carrying an infusion port and a collection port, said infusion port being positioned between the collection port and the first opening.

28. The device according to claim 26 wherein said first opening is positioned at a proximal end of the manifold hub, and a sidewall of the manifold hub extends between the first opening and a distal end of the manifold hub.

29. The device according to claim 28 wherein the distal end of the hub includes an opening in fluid communication with the inner lumen of the catheter, said sidewall includes a fluid infusion port for delivering fluid to the hub, and the first opening forms a collection port for collecting fluid from said manifold hub.

30. The device according to claim 28 wherein the distal end of the hub includes an opening in fluid communication with the inner lumen of the catheter, said sidewall includes a fluid collection port for receiving fluid from within the hub, and the first opening forms a fluid infusion port for delivering fluid to the hub.

31. The device according to claim 25 wherein the elongated member comprises a catheter having a distal end that can move between an open position and a closed position.

32. The device according to claim 31 wherein the distal end of the catheter has a first inner diameter when the end is in a closed position and a second, larger inner diameter when the end is in the open position.

33. The device according to claim 32 further comprising a mechanism for moving the distal end between the open and closed positions.

34. A ductal access device for accessing a breast duct and collecting cellular material from within the duct, said device comprising: an elongated member comprising a proximal end, a distal end and a lumen extending between the proximal and distal ends; a hub for being removably secured to said elongated member, said hub comprising an infusion port for delivering fluid to the catheter lumen, said infusion port being in fluid communication with an infusion device, and a collection port for receiving fluid and cellular material within the hub.

35. The device according to claim 34 wherein the lumen is open to the hub.

36. The device according to claim 35 wherein said collection port is in fluid communication with a fluid collection device.

37. The device according to claim 36 wherein the fluid collection device includes a source for creating negative pressure within the hub and a fluid collection line extending between said fluid collection port and the fluid collection device.

38. The device according to claim 35 further including a tubular member extending between said infusion port and the infusion device for delivering fluid from said infusion device to the hub.

39. The device according to claim 35 wherein the hub includes a distal end that is removably positioned within the proximal end of the elongated member.

40. A ductal access device for accessing a breast duct and collecting cellular material from within the duct, said device comprising a first elongated member having a first outer diameter sized for positioning within the breast duct and a second elongated member having a second outer diameter that is greater than said first outer diameter for preventing said second elongated member from entering the breast duct.

41. The device according to claim 40 wherein the first elongated member comprises a catheter having an internal lumen for introducing fluids into the breast duct and receiving fluid from within the breast duct.

42. The device according to claim 41 wherein said second elongated member comprises a hub including a lower port at a distal end for forming a fluid path with the internal lumen of the catheter.

43. The device according to claim 42 wherein the hub further includes first and second side ports spaced above the lower port.

44. The device according to claim 43 wherein the first and second side ports are at

the same height along a sidewall of the hub relative to the lower port.

45. The device according to claim 42 wherein the first and second side ports are at different heights along a sidewall of the hub relative to the lower port.

46. The device according to claim 41 wherein the catheter has an outer diameter of about 0.50 inch or less.

47. The device according to claim 46 wherein the outer diameter is in the range from about 0.010 inch to 0.050 inch.

48. The device according to claim 41 wherein the diameter of the inner lumen is about 0.007 inch or greater.

49. The device according to claim 42 further comprising an infusion tube connected to the first port of the hub; and a collection tube connected to the second port of the hub.

50. The device according to claim 42 wherein the manifold has a volume in the range from about 0.01 cc to 1.0 cc.

51. A ductal access device for accessing a breast duct and collecting cellular material from within the duct, said device comprising a first elongated member having a proximal end, a distal end and an internal lumen extending between said ends; a manifold hub having a proximal end and a distal end, said manifold hub having a lower opening for being in fluid communication with said inner lumen; and an elongated guide member for extending through at least one of the first elongated member and the hub for positioning a portion of the first elongated member in the breast duct.

52. The device according to claim 51 wherein the first elongated member comprises a catheter having a well at its proximal end.

53. The device according to claim 52 wherein said hub includes a distal end that is removably secured within said well after the catheter is positioned in the breast duct and the guide member has been removed from the internal lumen.

53. The device according to claim 53 wherein the distal end of the hub forms a luer lock fit with the well of the catheter.

54. The device according to claim 51 wherein the guide member includes a distal end having a plurality of openings.

55. The device according to claim 54 wherein said openings carry a medicament for administering to the lining of the breast duct.

56. A ductal access device for accessing a breast duct and collecting cellular material from within the duct, said device comprising a first elongated member having a distal end that can move between an open position and a closed position, a proximal end and an internal lumen extending between said ends and a manifold hub having a proximal end and a distal end, said manifold hub having a lower opening for being in fluid communication with said inner lumen.

57. The device according to claim 56 wherein the distal end of the elongated member has a first inner diameter when in the closed position and a second, larger diameter when in the open position.

58. The device according to claim 56 wherein said elongated member comprises a catheter, and further including a mechanism for moving the distal catheter opening between the open and closed positions.

59. The device according to claim 58 wherein said mechanism includes a wire extending between the proximal and distal ends of the catheter.

60. The device according to claim 57 wherein said distal end of the catheter is

formed of a shape memory material that opens in response to the application of a stimulus.

61. The device according to claim 60 wherein said stimulus includes heat or electric current.

62. The device according to claim 60 wherein said shape memory material is Nitinol.

63. A method for lavaging a ductal network in a human breast, said method comprising the steps of: inserting a distal end of a catheter having an internal lumen through a ductal orifice and into a distal lumen of the ductal network; infusing a lavage fluid into a manifold hub through an infusion port; introducing the lavage fluid into the ductal network; withdrawing the lavage fluid and substances borne by the lavage fluid from the ductal network; and delivering the withdrawn fluid and substances to a collection device through a collection port in the hub.

64. The method according to claim 63 where said step of infusing lavage fluid into the hub includes delivering the lavage fluid from an infusion device to the infusion port via an infusion tube.

65. The method according to claim 63 wherein the step of withdrawing the lavage fluid and substances includes the step of applying a negative pressure within the hub.

66. The method according to claim 65 wherein the negative pressure is applied by the collection device.

67. The method according to claim 65 wherein the method further includes the step of externally massaging the breast so that the fluid and substances are forced in the direction of the hub.

68. The method according to claim 63 wherein the step of delivering the fluid and substances to the collection device includes infusing fluid into the hub.

69. The method according to claim 63 wherein the step of introducing the lavage fluid into the ductal network includes the step of applying a positive fluid infusion pressure within the hub.

70. A method for obtaining cellular material from a mammalian breast duct network, said method comprising the steps of: inserting a distal end of an elongated device having an internal lumen through a ductal orifice and into a distal lumen of the ductal network; infusing a lavage fluid into a manifold hub through an infusion port; introducing the lavage fluid into the ductal network through the lumen; massaging an area of the breast; and delivering the lavage fluid and substances borne by the lavage fluid from the ductal network to a collection device through a collection port in the hub.

71. The method according to claim 70 further including the step of retaining at least 2 mils of the lavage fluid within the breast duct for a predetermined period of time.

72. The method according to claim 71 wherein the predetermined period of time is less than one second.

73. The method according to claim 71 wherein the predetermined period of time is between about one second and one hour.

74. The method according to claim 70 further including the step of creating a negative pressure in at least a portion of the hub.

75. The method according to claim 74 wherein the negative pressure is created by the collection device.

76. The method according to claim 70 wherein a collection tube extends between the collection port and the collection device.

77. The method according to claim 70 wherein the step of delivering the fluid and substances to the collection device includes infusing fluid into the hub.

78. The method according to claim 70 wherein the step of introducing the lavage fluid into the ductal network includes the step of applying a positive fluid infusion pressure within the hub.

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L18: Entry 7 of 34 File: PGPB Nov 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020173816
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020173816 A1

TITLE: Medical instrument with an atraumatic end

PUBLICATION-DATE: November 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, David	Belmont	CA	US	

US-CL-CURRENT: 606/194

CLAIMS:

1. A catheter for inserting in a body, said catheter comprising a proximal end, a distal end, a central section extending between said proximal end and said distal end and an internal lumen extending from said proximal end to said distal end through said central section, said distal end including a rigid bulbous tip with an outer diameter that is greater than an outer diameter of said central section.

2. The catheter according to claim 1 wherein said bulbous tip includes at least one substantially hemispherical section having a substantially circular cross section.

3. The catheter according to claim 1 further comprising an inner wall that defines said internal lumen, said bulbous tip includes an outer wall and the space between said inner wall and said outer wall is solid.

4. The catheter according to claim 1 wherein said bulbous end is free of any sharp edges that could score or perforate a portion of the body when the catheter is advanced within the body.

5. The catheter according to claim 1 wherein said bulbous tip includes first and second hemispherical sections separated by an equator that extends perpendicular to a longitudinal axis of the catheter.

6. The catheter according to claim 5 wherein said first hemispherical section is positioned between the second hemispherical section and the distal end of the catheter.

7. The catheter according to claim 6 wherein said first hemispherical section includes a basket for collecting samples from within the body.

8. The catheter according to claim 7 wherein said basket includes a plurality of elongated members spaced by openings that form a sample collection portion of the basket.

9. The catheter according to claim 1 further comprising an inner wall that defines said internal lumen and said bulbous tip includes an outer wall that is free of sharp edges.

10. The catheter according to claim 9 wherein the space between the inner wall and the outer wall includes a plurality of spaced internal supporting members each

separated from an adjacent one of the supporting members by a void.

11. The catheter according to claim 9 wherein the space between the inner wall and the outer wall is hollow.

12. The catheter according to claim 1 wherein said bulbous tip includes a substantially circular cross section.

13. The catheter according to claim 1 wherein the bulbous tip is integrally formed with the central section to form a continuous unitary structure.

14. The catheter according to claim 1 wherein the bulbous tip is substantially spherical.

15. A medical instrument for inserting into a body, said instrument comprising a proximal end, a distal end, a central section extending between said proximal and distal ends and an internal lumen extending from the proximal end to the distal end, said distal end including a portion having a outer diameter that is greater than an outer diameter of the central portion and having an outer wall being free of edges that could injure the body as the catheter is introduced or removed from the body.

16. The medical instrument according to claim 15 wherein said distal end portion has a substantially bulbous shaped tip.

17. The medical instrument according to claim 16 wherein said bulbous tip includes at least one substantially hemispherical section having a substantially circular cross section.

18. The medical instrument according to claim 15 wherein said medical instrument includes an inner wall that defines said internal lumen, said distal end portion includes an outer wall and the space between said inner wall and said outer wall is solid.

19. The medical instrument according to claim 15 wherein said distal end portion includes first and second hemispherical sections separated by an equator that extends perpendicular to a longitudinal axis of the medical instrument.

20. The medical instrument according to claim 19 wherein said first hemispherical section is positioned between the second hemispherical section and the distal end of the catheter.

21. The medical instrument according to claim 19 wherein said first hemispherical section includes a basket for collecting samples from within the body.

22. The medical instrument according to claim 21 wherein said basket includes a plurality of elongated members spaced by openings that form a sample collection portion of the basket.

23. The medical instrument according to claim 15 further comprising an inner wall that defines said internal lumen.

24. The medical instrument according to claim 23 wherein the space between the inner wall and the outer wall includes a plurality of spaced internal supporting members each separated from an adjacent one of the supporting members by a void.

25. The medical instrument according to claim 24 wherein the space between the inner wall and the outer wall is hollow.

26. The medical instrument according to claim 15 wherein said distal end portion includes a substantially circular cross section.

27. The medical instrument according to claim 26 wherein the bulbous tip is substantially spherical.

28. A medical instrument for inserting into a body, said instrument comprising a

proximal end, a distal end, a central section extending between said proximal and distal ends and a lumen extending from the proximal end to the distal end through the central section, said distal end including a rigid portion having a outer diameter that is greater than an outer diameter of the central portion.

29. The medical instrument according to claim 28 wherein said rigid portion has an outer wall being free of edges that could injure the body as the catheter is introduced or removed from the body.

30. The medical instrument according to claim 28 wherein said rigid portion has a substantially bulbous shaped tip.

31. The medical instrument according to claim 30 wherein said bulbous tip includes at least one substantially hemispherical section having a substantially circular cross section.

32. The medical instrument according to claim 28 wherein said medical instrument includes an inner wall that defines said lumen, said rigid portion includes an outer wall and the space between said inner wall and said outer wall is solid.

33. The medical instrument according to claim 28 wherein said distal end portion includes first and second hemispherical sections separated by an equator that extends perpendicular to a longitudinal axis of the medical instrument.

34. The medical instrument according to claim 33 wherein said first hemispherical section is positioned between the second hemispherical section and the distal end of the catheter.

35. The medical instrument according to claim 34 wherein said first hemispherical section includes a basket for collecting samples from within the body.

36. The medical instrument according to claim 35 wherein said basket includes a plurality of elongated members spaced by openings that form a sample collection portion of the basket.

37. The medical instrument according to claim 28 further comprising an inner wall that defines said lumen and said rigid portion includes an outer wall that is free of sharp edges.

38. The medical instrument according to claim 37 wherein the space between the inner wall and the outer wall includes a plurality of spaced internal supporting members each separated from an adjacent one of the supporting members by a void.

39. The medical instrument according to claim 37 wherein the space between the inner wall and the outer wall is hollow.

40. The medical instrument according to claim 28 wherein said rigid portion includes a bulbous tip with a substantially circular cross section.

41. The medical instrument according to claim 40 wherein the bulbous tip is substantially spherical.

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L18: Entry 6 of 34 File: PGPB Dec 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020193822
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020193822 A1

TITLE: Externally positioned medical dilator

PUBLICATION-DATE: December 19, 2002

INVENTOR-INFORMATION:

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Schulz, Grace	San Carlos	CA	US	
Patel, Tina	San Mateo	CA	US	

US-CL-CURRENT: 606/198; 606/108, 606/191

CLAIMS:

We claim:

1. An expandable medical dilator for dilating a body opening during or in preparation for the performance of a medical procedure, said dilator comprising an outer wall for positioning against an inner surface of the body opening as the opening is being dilated, an inner wall defining an internal lumen for receiving a medical instrument being used to perform the medical procedure and at least one expansion region.

2. The expandable dilator according to claim 1 wherein said dilator comprises a proximal end and a distal end, and said outer wall tapers from a position along the length of the dilator to the distal end.

3. The expandable dilator according to claim 2 wherein said at least one expansion region extends along at least a portion of the length of said dilator.

4. The expandable dilator according to claim 3 wherein each expansion region is defined by at least one opening in said dilator, said at least one opening being defined by opposing wall surfaces that extend between said inner wall and said outer wall.

5. The expandable dilator according to claim 3 wherein each expansion region includes at least one tear away region.

6. The expandable dilator according to claim 5 wherein each tear away region includes a plurality of spaced perforations.

7. The expandable dilator according to claim 4 wherein said at least one opening includes a plurality of openings spaced around the circumference of the dilator.

8. The expandable dilator according to claim 4 wherein said at least one opening extends along the length of said dilator from said proximal end to said distal end.

9. The expandable dilator according to claim 4 wherein said at least one opening

extends from a position spaced from said proximal end to said distal end.

10. The expandable dilator according to claim 1 wherein said inner wall tapers from a position along its length to said distal end.

11. The expandable dilator according to claim 1 wherein said distal end has a first outer diameter before the medical instrument is inserted and a second, larger outer diameter after the medical instrument has been introduced at said distal end.

12. The expandable dilator according to claim 1 further including a beveled surface positioned between said proximal end and said distal end.

13. The expandable dilator according to claim 12 wherein a portion of said outer wall defines a substantially cylindrical portion of the dilator, and said beveled surface extends between a distal end of said cylindrical portion and said distal end of said dilator.

14. The expandable dilator according to claim 13 wherein said cylindrical portion includes an expansion region extending along at least a portion of its length.

15. The expandable dilator according to claim 14 wherein said expansion region includes at least one opening defined by opposing wall surfaces that extend between said inner and outer walls.

16. The expandable dilator according to claim 14 wherein said expansion region includes at least one tear away region.

17. The expandable dilator according to claim 16 wherein said tear away region includes a plurality of spaced perforations.

18. The expandable dilator according to claim 14 wherein said expansion region extends along said cylindrical portion from the proximal end of the dilator to the distal end of the cylindrical portion.

19. The expandable dilator according to claim 12 further including a guide member that extends longitudinally away from said distal end.

20. The expandable dilator according to claim 1 further including an expansion region along one side of said internal lumen and a hinge along an opposite side of said internal lumen.

21. The expandable dilator according to claim 1 wherein said dilator further includes a member extending away from a longitudinal axis of the dilator for preventing said dilator from completely entering the body.

22. The expandable dilator according to claim 21 wherein said member includes a wing for securing to a portion of the body.

23. The expandable dilator according to claim 21 wherein said member includes a step along a portion of said outer wall.

24. An expandable dilator for being positioned within a body opening and internally receiving at least a portion of a medical instrument, said expandable dilator comprising a proximal end and a distal end, an inner wall defining an inner lumen for receiving the medical instrument, said inner lumen extending between said proximal end and said distal end and having a tapered region that extends from a position along said inner wall to said distal end, and an outer wall having a tapered region that extends from a position along said outer wall to said distal end; and at least one expansion region extending along at least a portion of the dilator so that the distal end can expand in response to the introduction of the medical instrument.

25. The expandable dilator according to claim 24 further comprising a stop member for preventing the dilator from extending into the body beyond a predetermined distance.

26. The expandable dilator according to claim 24 wherein said expansion region is defined by at least one opening in said dilator, said at least one opening being defined by opposing wall surfaces that extend between said inner wall and said outer wall.

27. The expandable dilator according to claim 26 wherein said at least one opening extends along the length of said dilator from the said proximal end to said distal end.

28. The expandable dilator according to claim 26 wherein said at least one opening extends from a position spaced from said proximal end to said distal end.

29. The expandable dilator according to claim 24 wherein said dilator comprises a plurality of expansion regions, each said expansion region including an opening defined by opposing wall surfaces that extend between the inner wall and the outer wall.

30. The expandable dilator according to claim 24 wherein said expansion region includes at least one tear away region.

31. The expandable dilator according to claim 30 wherein each tear away region includes a plurality of spaced perforations.

32. The expandable dilator according to claim 24 wherein said dilator comprises a plurality of expansion regions each including a plurality of spaced perforations.

33. The expandable dilator according to claim 24 wherein said inner wall tapers from a position along its length to said distal end.

34. The expandable dilator according to claim 24 wherein said distal end has a first outer diameter before the medical instrument is inserted and a second, larger outer diameter after the medical instrument has been introduced at said distal end.

35. A medical dilator for positioning within and dilating a passageway in a body before or during a medical procedure, said medical dilator comprising: a distal end for positioning within the body and a proximal end opposite said distal end; and an expansion region extending along at least a portion of said dilator between said proximal end and said distal end, wherein said expansion region expands at least a portion of said dilator as a medical instrument is introduced into said dilator.

36. The medical dilator according to claim 35 further comprising beveled surface extending at an angle to a longitudinal axis of the dilator.

37. The medical dilator according to claim 36 further comprising a cylindrical portion extending between said beveled surface and said proximal end.

38. The medical dilator according to claim 37 wherein said expansion region extends along at least a portion of said cylindrical portion.

39. The medical dilator according to claim 38 wherein said expansion region extends from said proximal end to said beveled surface.

40. The medical dilator according to claim 36 further comprising a guiding member extending from said distal end away from said beveled surface.

41. The medical dilator according to claim 35 wherein said expansion region is defined by at least one opening in said dilator, said at least one opening being defined by opposing wall surfaces that extend between an inner wall that defines a lumen with the dilator and an outer wall.

42. The medical dilator according to claim 35 wherein said expansion region includes at least one tear away region.

43. The medical dilator according to claim 42 wherein said tear away region includes

a plurality of spaced perforations.

44. The medical dilator according to claim 35 wherein said expansion region extends from the proximal end of said dilator to the distal end of said dilator.

45. The medical dilator according to claim 35 wherein the distal end of said dilator has a first outer diameter before the medical instrument is inserted and a second, larger outer diameter after the medical instrument has been introduced at said distal end.

46. The medical dilator according to claim 35 wherein said dilator further includes a member extending away from longitudinal axis of the dilator for preventing said dilator from completely entering the body.

47. The medical dilator according to claim 46 wherein said member includes a wing for securing to a portion of the body.

48. The medical dilator according to claim 47 wherein said member includes a step along a portion of an outer wall.

49. A method of dilating an opening in a body, said method comprising the steps of: positioning an expandable dilator within the body through the opening; introducing a medical instrument into an inner lumen of said expandable dilator; expanding a distal end of said dilator; and dilating said body opening.

50. The method according to claim 49 wherein the medical instrument is advanced into the body through the inner lumen of the dilator so that the instrument is free of contact with the body while positioned within said lumen.

51. The method according to claim 49 wherein said step of expanding the distal end includes advancing the medical instrument into a tapered region of the inner lumen.

52. The method according to claim 51 wherein said expanding step includes separating opposing wall surfaces that form an opening along the length of the lumen, said wall surfaces extend between the inner lumen and an outer surface of the dilator.

53. The method according to claim 51 further including the step of removing the dilator from within the body by sliding the dilator in the direction of a proximal end of the medical instrument.

54. The method according to claim 51 wherein said expanding step includes opening a tear away region along a length of the dilator.

55. The method according to claim 54 where said opening step includes tearing a plurality of connections between adjacent perforations along the length of the dilator.

56. The method according to claim 54 further including the step of removing a first portion of the dilator from within the body and then removing a second portion of the dilator from within the body.

57. The method according to claim 49 further including the step of positioning the medical instrument in a passageway within the body.

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L18: Entry 5 of 34 File: PGPB Jan 30, 2003

PGPUB-DOCUMENT-NUMBER: 20030021787
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030021787 A1

TITLE: Method and devices for delivery of agents to breast milk ducts

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Olsen, Philip M.	Mountain View	CA	US	

US-CL-CURRENT: 424/155.1; 435/6, 435/7.23, 604/42

CLAIMS:

What is claimed is:

1. A method of treating a breast condition comprising: establishing a temporary access track to a breast milk duct; and delivering an agent through the track to the duct over time wherein over a defined period of time a specific amount of agent is delivered at a relatively constant rate.

2. A method as in claim 1, wherein the condition arises in a breast milk duct or terminal ductal lobular unit.

3. A method as in claim 1, wherein the condition comprises a breast precancer or cancer.

4. A method as in claim 1, wherein the temporary access track comprises a lumen in the breast milk duct.

5. A method as in claim 4, wherein the agent comprises a time-release formulation.

6. A method as in claim 1, wherein establishing a track comprises placing an indwelling unit comprising a reservoir in the breast duct with a lead or tube to the nipple surface for retrieving or reloading the unit.

7. A method as in claim 6, wherein placing the indwelling unit comprises placing the unit in the lactiferous sinus.

8. A method as in claim 6, wherein the indwelling unit comprises a pump.

9. A method as in claim 8, wherein the pump is osmotic.

10. A method as in claim 6, wherein the indwelling unit comprises a microchip.

11. A method of treating a breast condition comprising: placing an implant into a breast during breast surgery, wherein the implant comprises a reservoir, and delivering an agent from the reservoir to the duct over time wherein over a defined period of time a specific amount of agent is delivered at a relatively constant rate.

12. A method as in claim 11, wherein the reservoir comprises a time release formulation or a biodegradable material.

13. A method as in claim 11, wherein the reservoir comprises a pump or a microchip.

14. A method as in claim 13, wherein the reservoir is a pump and the pump is osmotic.

15. A method as in claim 13, further comprising establishing a temporary access track to a breast milk duct so that the pump can be accessed from the nipple surface after surgery.

16. A method of treating a breast condition comprising: accessing a breast milk duct; and delivering an agent comprising a time release formulation to the duct over time, wherein over a defined period of time a specific amount of agent is delivered at a relatively constant rate.

17. A method as in claim 16, wherein the time-release formulation comprises a biodegradable material.

18. A device for delivering an agent to a breast milk duct over time comprising: a reservoir capable of dwelling in the duct or on the nipple surface, and a line or tube connected to the reservoir to deliver agent to the duct, reload an indwelling reservoir when empty, or provide retrieval of an indwelling reservoir from the duct, wherein the reservoir releases agent to the duct over time.

19. A device as in claim 18, wherein an empty indwelling reservoir can be reloaded through the line or tube.

20. A device as in claim 18, wherein the reservoir comprises a pump.

21. A device as in claim 20, wherein the pump is osmotic.

22. A device as in claim 18, wherein the reservoir holds a volume of agent in the range of from about 0.001 ml to 10 ml.

23. A device as in claim 18, wherein the reservoir delivers a volume of agent at a rate in a range from about 0.0001 ml/day to about 0.001 ml/hour.

24. A device as in claim 18, wherein the reservoir comprises a microchip.

25. A kit comprising a device of any of claims 18-24 and instructions for use.

26. A kit comprising a device of any of the claims 18-24, instructions for use, and further comprising an agent for delivery to a breast duct using the device.

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CLAIMS:

What is claimed is:

1. A method of identifying the location of premalignant or malignant breast cancer within a mammalian body comprising a breast duct or breast ductal network, said method comprising: providing a coupled compound comprising a targeting molecule coupled to an identifying agent; delivering the coupled compound through a preselected individual breast duct in an amount sufficient to identify premalignant or malignant cancerous cells; identifying any bound cells; and allowing any unbound coupled compound to clear in the body; wherein any coupled compound that does not bind a cell in the duct diffuses out of the breast ductal network and is absorbed and cleared in the body without requiring removal by a practitioner of the unbound coupled compound.

2. A method as in claim 1, wherein delivering comprises cannulation or catheterization of the breast duct.

3. A method as in claim 1, wherein the coupled compound is delivered to more than one duct on a breast.

4. A method as in claim 1, wherein the cells are identified for the purpose of excising tissue surrounding and including the cells.

5. A method as in claim 1, wherein the targeting agent comprises an agent selected from the group consisting of a protein, a polypeptide, a peptide, an antibody, an antibody fragment, a F(ab') fragment of an antibody, a F(ab').sub.2 fragment of an antibody, an Fc portion of an antibody, a heavy chain of an antibody, a light chain of an antibody, a humanized antibody, a humanized antibody fragment, a ligand, a receptor, a drug, a chemical, a lipid, a liposome, a small molecule, and a nucleic acid.

6. A method as in claim 5, wherein the targeting agent is a small molecule and the small molecule is sestamibi.

7. A method of identifying the location of premalignant or malignant breast cancer

within a mammalian body comprising a breast duct or breast ductal network, said method comprising: providing a identifying agent which binds to premalignant and/or malignant ductal cells; and delivering the identifying agent through a preselected individual breast duct in an amount sufficient to bind to and identify premalignant or malignant cancerous cells; identifying any bound cells; and allowing any unbound identifying agent to clear in the body; wherein any identifying agent that does not bind a cell in the duct diffuses out of the breast ductal network and is absorbed and cleared by the body without requiring removal by a practitioner of the unbound identifying agent.

8. A method as in claim 7, wherein delivering comprises cannulation or catheterization of the breast duct.

9. A method as in claim 7, wherein the identifying agent is delivered to more than one duct on a breast.

10. A method as in claim 7, wherein the cells are identified for the purpose of excising tissue surrounding and including the cells.

11. A method as in claim 7, wherein the identifying agent comprises an agent selected from the group consisting of a protein, a polypeptide, a peptide, an antibody, an antibody fragment, a F(ab') fragment of an antibody, a F(ab').sub.2 fragment of an antibody, an Fc portion of an antibody, a heavy chain of an antibody, a light chain of an antibody, a humanized antibody, a humanized antibody fragment, a ligand, a receptor, a drug, a chemical, a lipid, a liposome, a small molecule, and a nucleic acid.

12. A method of treating premalignant or malignant breast cancer located within a mammalian body, said method comprising: providing a coupled compound comprising targeting molecule coupled to a therapeutic agent; and delivering the coupled compound through a preselected individual breast duct in an amount sufficient to inhibit proliferation of the cancerous cells; and allowing unbound coupled compound to clear through the body; wherein any coupled compound that does not bind a cell in the duct diffuses out of the breast ductal network and is absorbed and cleared by the body without requiring removal by a practitioner of the unbound coupled compound.

13. A method as in claim 12, wherein delivering comprises cannulation or catheterization of the breast duct.

14. A method as in claim 12, wherein the coupled compound is delivered to more than one duct on a breast.

15. A method as in claim 12, wherein the targeting agent comprises an agent selected from the group consisting of a protein, a polypeptide, a peptide, an antibody, an antibody fragment, a F(ab') fragment of an antibody, a F(ab').sub.2 fragment of an antibody, an Fc portion of an antibody, a heavy chain of an antibody, a light chain of an antibody, a humanized antibody, a humanized antibody fragment, a ligand, a receptor, a drug, a chemical, a lipid, a liposome, a small molecule, and a nucleic acid.

16. A method as in claim 15, wherein the targeting agent comprises a small molecule and the small molecule is sestamibi.

17. A method as in claim 12, wherein the therapeutic agent is selected from the group consisting of a cytotoxic agent, a cytolytic agent, a cytostatic agent, a growth inhibiting agent, an antagonist, an agonist, and a drug or agent containing liposome.

18. A method as in claim 12, wherein the therapeutic agent comprises an agent with therapeutic activity against cancerous or precancerous cells that can be coupled to a targeting agent.

19. A method of treating a premalignant or malignant breast cancer located within a mammalian body, said method comprising: providing a targeting molecule itself having

therapeutic activity; and delivering the targeting molecule through a preselected individual breast duct in an amount sufficient to inhibit proliferation of the premalignant or malignant cells, wherein at least a portion of the targeting molecule binds to premalignant or malignant cells; and allowing unbound targeting molecule to clear through the body; wherein any targeting molecule that does not bind a cell in the duct diffuses out of the breast ductal network and is absorbed and cleared by the body without requiring removal by a practitioner of the targeting molecule.

20. A method as in claim 19, wherein delivering comprises cannulation or catheterization of the breast duct.

21. A method as in claim 19, wherein the targeting molecule is delivered to more than one duct on a breast.

22. A method as in claim 19, wherein the targeting molecule comprises an agent selected from the group consisting of a protein, a polypeptide, a peptide, an antibody, an antibody fragment, a F(ab') fragment of an antibody, a F(ab').sub.2 fragment of an antibody, an Fc portion of an antibody, a heavy chain of an antibody, a light chain of an antibody, a humanized antibody, a humanized antibody fragment, a ligand, a receptor, a drug, a chemical, a lipid, a liposome, a small molecule, and a nucleic acid.

23. A method as in claim 22, wherein the targeting molecule comprises a small molecule, and the small molecule is sestamibi.

24. A method as in claim 19, wherein the therapeutic activity is selected from the group consisting of a cytotoxicity, a cytolytic activity, cytostatic activity, growth inhibition, antagonism, an agonism, and immunotoxicity.

25. A method as in claim 19, wherein the therapeutic activity is effective against cancerous or precancerous cells.

26. A method as in claim 12 or 19, wherein the premalignant or malignant breast cancer comprises cells having a stage selected from the group consisting of hyperplasia, atypical hyperplasia, low-grade ductal carcinoma in situ, high-grade ductal carcinoma in situ, and invasive carcinoma.

27. A kit for localizing or treating lesions in a breast duct, said kits comprising: at least one catheter configured to access a ductal network in a human breast; and instructions for use setting forth a method according to any of claims 1 to 26.

28. A kit as in claim 27, further comprising at least one container holding a reagent which is used in the method being performed with the kit.

29. A kit as in claim 27, further comprising a package holding the catheter and the instructions for use.

30. A kit as in claim 27, further comprising a reagent, wherein the reagent comprises an agent comprising at least a portion selected from the group consisting of a protein, a polypeptide, a peptide, an antibody, an antibody fragment, a F(ab') fragment of an antibody, a F(ab').sub.2 fragment of an antibody, an Fc portion of an antibody, a heavy chain of an antibody, a light chain of an antibody, a humanized antibody, a humanized antibody fragment, a ligand, a receptor, a drug, a chemical, a lipid, a liposome, a small molecule, and a nucleic acid.